FOCUS

on

LATE-LIFE MENTAL HEALTH

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“The Brain & Behavior Research Foundation Scientific Council has grown to include 132 volunteer members, each of whom bring special skills and unique knowledge bases that cover every aspect of brain and behavior research. The reach of the Brain & Behavior Research Foundation support extends to the world’s leading medical research and care facilities. Our effort knows no borders. The impact of our effort is not only in the development of promising scientists, but also in the focus it brings to the challenge and urgent need of bringing hope and better lives to all those living with mental illness.”

Herbert Pardes, M.D.
President, Scientific Council
President & CEO, NewYork-Presbyterian Hospital

Scientific Council

President  Herbert Pardes, M.D.
Vice President Emeritus  Floyd E. Bloom, M.D.
Dear Friends,

This is a very special year for us at the Brain & Behavior Research Foundation as we begin our 25th year of awarding NARSAD Grants leading to advances and breakthroughs in scientific research. NARSAD was formed with a vision of dramatically accelerated investments to better understand the causes of mental illness, develop better treatments and improve lives. Since that time more than 4,000 NARSAD Grants have been funded—with almost $300 million of donor contributions—to scientists around the world. This investment has shaped the psychiatric field and enabled countless discoveries that are paving the road to curing the diseases of the brain.

We open this issue of The Quarterly with highlights of some of the most recent discoveries in 2011. They reflect the breadth of the research we fund, across mental illnesses and across research disciplines. We then turn to our theme of ‘late-life mental health’ with a profile interview of Nobel Prizewinner Eric R. Kandel, M.D., longtime Brain & Behavior Research Foundation Scientific Council Member and three-time NARSAD Distinguished Investigator Grantee. He speaks of the aging brain, emphasizing its plasticity and capacity to continually learn and adapt, and expresses the critical importance of the Foundation’s support of the field.

We visit the personal story of Janet Larsen, who shares the journey of her father’s mental illness and how its late onset was handled more than 40 years ago. With her story, we can appreciate the advances made in understanding mental illnesses, the development of diagnostic tools and the improved treatments available today. It also reminds us of the progress being made in dealing with these illnesses as diseases of the brain, akin to the many diseases of the body. With increased knowledge, the stigma of mental illness, too familiar to too many families, is slowly being chipped away.

In ‘Meet a Distinguished Investigator’, Dr. Dilip V. Jeste, one of the world’s foremost experts on geriatric psychiatry, shares his perspective. He explains what drew him to the field, highlights the key challenges of late-life mental health and expresses his deep wish for the full recognition in society that those in late life (with or without mental illness) are invaluable resources in their wealth of experience and wisdom.

Throughout 2012 we will share more about our 25-years of unparalleled contributions and commitment to the field of brain and behavior research. We count on you to join our Campaign for Productive Lives with your recommitment to, once again, accelerate the momentum, build upon the substantial foundation made to date and support the brilliant minds working to improve the lives of all those suffering.

Thank you for continuing the journey with us. The momentum is great and there is so much work yet to be done.

Yours sincerely,

Benita Shobe
President & CEO

www.bbrfoundation.org
New Technologies: Depression
Tarique Perera, M.D., furthers studies on Transcranial Magnetic Stimulation (TMS), pioneered by Mark S. George, M.D. Dr. George estimates that three people a day are recovering from depression because of TMS.

Diagnostic Tools / Early Intervention: Depression
Andrea Danese, M.D., Ph.D., and colleagues discover that people mistreated in childhood are twice as likely to suffer depression and respond poorly to treatment, leading the way toward diagnostic and early intervention possibilities for those at risk.

Basic Research: Schizophrenia and Bipolar
Jonathan Mill, Ph.D., and colleagues demonstrate that potentially reversible epigenetic changes play a key role in mental illness in the first study to systematically investigate genome-wide epigenetic differences in a large number of psychosis discordant twin-pairs.

Next Generation Therapies: Schizophrenia
Aaron T. Beck, M.D., and colleagues demonstrate that cognitive behavioral therapy (CBT) can successfully treat the ‘negative’ symptoms of schizophrenia, such as emotional flatness, listlessness and isolation.

Basic Research: Schizophrenia

Diagnostic Tools / Early Intervention: Depression
Joan L. Luby, M.D., and colleagues successfully tested a novel form of psychotherapy called Parent Child Interaction Therapy-Emotion Development (PCIT-ED) to help preschoolers with symptoms of depression function better and learn to regulate their emotions.

Next Generation Therapies: Depression and Bipolar
Carlos A. Zarate, M.D., pioneered research on rapid-acting antidepressants, such as ketamine, demonstrating rapid antidepressant effects in treatment-resistant patients with depression and bipolar disorder.

Basic Research: OCD
Stephanie Dulawa, Ph.D., and colleagues isolated a single neurotransmitter receptor in a specific brain region responsible for OCD-like symptoms, offering a new avenue for developing better treatments in a disease where there is only one successful therapy to date.

Basic Research: Autism
Schahram Akbarian, M.D., Ph.D., and colleagues were the first to map epigenetic changes in neurons from the brains of individuals with autism, providing empirical evidence that epigenetic alterations—changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence—may play an important role in the disease.

Basic Research: Anxiety, PTSD
Michael Fanselow, Ph.D., and Stephanie Bissiere, Ph.D., were part of a team that uncovered a previously unexplored target for anti-anxiety treatments—gap junctions in the brain, which, if blocked with drugs, could prevent fear memories from forming.

Visit our website to read more:
bbrfoundation.org
Paola Dazzan, M.D., who leads early psychosis research at the Institute of Psychiatry, King’s College London, has pursued the goal of applying neuroimaging to the study of psychosis with support from three NARSAD Grants. In this most recent work, she, and King’s College and University College London colleague Dr. Janaina Mourao-Miranda, led a multi-institutional collaboration in the UK.

Dr. Dazzan has been seeking to find a reliable way to predict how psychotic illness will develop after a first psychotic break. What currently happens can range from recovery with minimal symptoms to the opposite extreme of persistent psychosis with serious cognitive and functional loss. Delusions and hallucinations are the hallmark symptoms of schizophrenia and can occur in some other mental illnesses as well, but there has been no way of knowing what course a psychotic illness will take in a particular individual. This inability to predict a patient’s future illness has made it difficult to know what treatment to prescribe.

In recent years, the introduction of magnetic resonance imaging (MRI) has made it possible to visualize brain structure, but the neuroanatomical changes that occur in early psychosis are too subtle for standard MRI to be useful diagnostically. Now, a study conducted by Dr. Dazzan and colleagues has provided preliminary evidence that an innovative technique to evaluate MRI, called support vector machine (SVM) MRI, can be used to predict the course of illness. Reporting in the Nov. 7 online edition of the journal Psychological Medicine, the scientists state that if validated in larger trials, their finding “could enable targeted clinical decisions based on imaging data.”

“This is the first step towards being able to use brain imaging to provide tangible benefit to patients affected by psychosis,” says Dr. Dazzan. “This could offer a fast and reliable way of predicting the outcome for an individual patient, allowing us to optimize treatments for those most in need, while avoiding long-term exposure to antipsychotic medications in those with mild forms.”

The researchers began by making MRI scans of 100 patients at the time of their first psychotic episode and of 91 healthy controls. The patients were then re-examined six years later and classified as having experienced a continuous, episodic or intermediate course of illness. The team then applied SVM to these MRI scans to study changes in brain structure, creating computer algorithms that could identify, at the time of this first scan, patients who would then experience long periods of remission and those who would remain continuously unwell. Algorithms that quantify risk of future episodes of disease are common in other medical areas, such as cardiovascular medicine and oncology, but have not been available for mental illnesses.

According to Dr. Dazzan, the technique she and her group have refined is easy to apply—a ten-minute test that could be incorporated into routine clinical investigations. “The information this provides,” she states, “could help inform the treatment options available to each patient and help us better manage their illness.”
The Quarterly
Research Discoveries in the News

Joel E. Kleinman, M.D., Ph.D., winner of the Brain & Behavior Research Foundation Lieber Prize for Outstanding Achievement in Schizophrenia Research in 2011, is working to unravel the mystery of what goes awry in the brain—and how—to cause mental illness. Chief of the Section on Neuropathology and deputy chief of the Clinical Brain Disorders Branch in the Genes, Cognition and Psychosis Program at the National Institute of Mental Health (NIMH), he has for over three decades studied the molecular biology of brain development and disorders, particularly schizophrenia, for which he has amassed one of the most important collections of postmortem human brains.

Dr. Kleinman’s latest research is helping to resolve a primary question in neuroscience: when and where different genes are expressed—turned on—in the brain over the course of a lifetime. He and his team studied 269 postmortem healthy brains ranging from 14 days prenatal to 80 years of age, developing a database of one trillion pieces of information. The findings, reported in the Oct. 26 issue of the journal Nature, along with the results of a second landmark study on the subject, have important implications for understanding the timeline and genetic variation involved in mental illness.

In the process of gene expression, genes, made of DNA, are transcribed by another molecule called messenger RNA, or mRNA. The messages mRNA transcripts carry are a direct production of the proteins that perform life’s functions. Each gene can make several mRNA transcripts expressed in patterns influenced by some 1.5 million DNA variations unique to each person. This set of transcripts, the transcriptome, is each individual’s molecular signature.

The databases Dr. Kleinman and colleagues have created now allow neuroscientists to examine how genetic variation is associated with the expression of mRNA in the brain across the lifespan. Dr. Kleinman’s laboratory has focused on the prefrontal cortex, the region responsible for higher brain functions, such as planning and judgment. He says: “Our study shows how 650,000 common genetic variations that make each of us a unique person may influence the ebb and flow of 24,000 genes in the most distinctly human part of our brain as we grow and age.”

The research revealed, among other things, rapid gene expression during fetal development that slows abruptly after birth, levels off in middle age, and then surges anew in old age. In previous studies, Dr. Kleinman had found that all genetic variations implicated to date in schizophrenia are associated with transcripts expressed in the fetal brain. Current research seems to point to a contrasting situation for affective disorders, such as depression, which may be associated with transcripts later in life. Dr. Kleinman and his colleagues are continuing and expanding their research to include all transcripts of all human genes, examining 1,000 postmortem brains, including brains of people who had schizophrenia and other brain disorders.

NIMH Director Thomas R. Insel, M.D., states: “Having at our fingertips detailed information about when and where specific gene products are expressed in the brain brings new hope for understanding how this process can go awry in schizophrenia, autism and other brain disorders.”

Groundbreaking Genetic Research Helps Identify How and When the Brain May Produce Mental Illness

Joel E. Kleinman, M.D., Ph.D.
Imagine that you are standing on a busy city street corner and you gather together the first 100 passersby who are precisely 70 years old. “In this randomly selected group, let’s assume that men and women are equally represented and that none of them appears to be suffering from any major illnesses, including any kind of cognitive impairment.”

The speaker is Dr. Eric Kandel, NARSAD Distinguished Investigator Grantee and member of the Brain & Behavior Research Foundation Scientific Council, whose seminal discoveries about the biological basis of memory earned him a Nobel Prize in 2000.

“If we were to measure these one hundred 70-year-olds with very sensitive indices of cognitive function, we’d discover that 40 of them have memory comparable to what they had when they were in their forties.” This, says Dr. Kandel, “is what we call ‘successful aging.’”

And the remaining 60? Extremely sensitive tests would reveal that these individuals were destined to have one or another form of cognitive impairment.

“It’s roughly half and half in this group of 60,” explains Dr. Kandel. “About 30 will have a mild, age-related type of memory decline, which usually takes the form of forgetting the names of people or where one has placed the house keys—information that does come back and can be remembered, just not immediately. This kind of age-related memory loss is relatively benign, even though it’s a source of frustration and does tend to progress, to varying degrees.”

We have accounted, then, for 70 people in the randomly selected group: 40 are in good shape and 30 have begun a gradual and moderate decline that typically affects short-term memory. The remaining 30 people, on average, will go on to develop Alzheimer’s disease, “which is a truly devastating, progressive illness that involves severe memory loss, impairments in language, motor coordination and other brain functions.” Dr. Kandel clarifies that among this unlucky 30 percent, the
biological processes that lead to Alzheimer’s will typically have begun by age 70 although symptoms may not appear for years.

Dr. Kandel—who is familiar to many non-scientists as Charlie Rose’s co-host in Mr. Rose’s ‘The Brain Series’ on PBS—and members of the Kandel laboratory group at Columbia University perform research that has uncovered some of the key molecular and genetic processes that give rise to memory as well as to the loss of memory. The intellectual roots of this work can be traced back half a century, to a time when Dr. Kandel made the fateful, and for us, fortunate decision to shift his focus from psychiatry to neuroscience.

As told in his award-winning autobiography, In Search of Memory (2006), his growing interest in the biological basis of memory mirrors (and in some ways foreshadows) the progress of an entire field. Or, more exactly, the converging of two fields that traditionally had stood apart from one another. “If you step back a bit, to the 1950s, you realize that what really distinguished psychiatry from neuroscience was its overwhelmingly clinical focus. At that time, relatively little work had been done on the basic biology of psychiatric disorders.”

For a variety of fascinating reasons explained in novelistic detail in his book, Dr. Kandel in the early 1960s became determined to use rapidly evolving technologies to trace and record neural impulses, and thereby to determine the precise mechanisms of individual neural circuits. As he turned his experimentation to the mechanisms of memory formation, he decided to use as his model the large marine snail called Aplysia californica, hoping not only to show that this comparatively simple animal could learn to avoid unpleasant stimuli, but also to show at the level of cells and circuits how it learned. He wanted, in other words, to understand how experience-related memories were formed and retained for later recall.

Now famous in the annals of science, these experiments sent Dr. Kandel’s career on a magnificent trajectory. He points out that beginning in the 1980s, his NARSAD Grant played a vital role in extending and vastly broadening the type of research that his team pioneered…“The Brain & Behavior Research Foundation, through its NARSAD Grants, has made an extraordinary contribution, not only in providing funds for psychiatric research but in helping to structure the field,” he says.

Dr. Kandel points out that beginning in the 1980s, his NARSAD Grant played a vital role in extending and vastly broadening the type of research that his team pioneered…“The Brain & Behavior Research Foundation, through its NARSAD Grants, has made an extraordinary contribution, not only in providing funds for psychiatric research but in helping to structure the field,” he says. Just in the last year, his team at Columbia has succeeded in creating a new line of mice that model the problems of motivation seen in people with schizophrenia. “Motivation has two components, ‘wanting’ and ‘liking,’” Dr. Kandel explains. “If you ask a person with schizophrenia to come to your house for dinner, he will typically refuse, saying it’s too much trouble. They don’t want to put out the effort. But if you drag them to your house and serve a nice dinner, you notice that they enjoy it as much as you and I. They enjoy the experience, but don’t tend to seek it out.

Interview with a Researcher

“There is a consensus that you can do certain things…staying physically fit, seeing your physicians, following their advice…staying socially engaged; staying intellectually engaged.”
"We found to our amazement that you can test for wanting and liking in the mouse. In our mouse that models this aspect of schizophrenia, they ‘like’ things as much as healthy mice; but they have a terrific deficit in ‘wanting.’ When I presented this data recently at Johns Hopkins, a man in the audience later came over to me and said, ‘My son is just like your mouse!’ It was an extraordinary moment!"

At 82, Dr. Kandel has lost nothing of his mental acuity, none of his intellectual curiosity, and not a bit of his sense of humor (his signature guffaw still can set an entire room into peals of laughter). Scientific discoveries provide him with the same intoxicating rush of excitement and satisfaction that they did years ago. And this raises an important point about aging and memory loss.

"There is a consensus that you can do certain things to prevent non-Alzheimer’s age-related memory loss,” he points out. “It’s agreed that good health is important. Staying physically fit, seeing your physicians, following their advice. Getting your blood pressure under control—and if you have diabetes, getting it under control. Getting your lipid levels under control. Staying physically active by doing exercise, staying socially engaged; staying intellectually engaged.”

In other words: “you lose it if you don’t use it”? That does indeed appear to be true, Dr. Kandel says, specifying that mental exercises involving doing things you have not previously done—say, for instance, memorizing poetry—can really help as you enter old age. This can act as a prophylactic for non-Alzheimer’s age-related memory loss, he says. As for Alzheimer’s, it is not at all certain that any of these things will help.

Plaque-like accumulations of proteins—beta-amyloid proteins, specifically—have long been associated with the occurrence of Alzheimer’s and have been found to be prevalent in the brains of those who have died with the illness. Recent attempts to develop drugs to break up these sheet-like plaques in humans have failed, however. Animal models are a step forward. “You can take a mutated gene that gives rise to these plaques, place it in a mouse, and they will develop early-stage Alzheimer’s,” says Dr. Kandel. But the illness in humans takes about 10 years to develop once plaques begin to appear. That progression hasn’t yet been modeled successfully in mice.

He speculates that the drugs used so far in human trials may have failed because they have been given too late—years after the plaques have begun to accumulate. On the other hand, an approach other than attacking the plaques may be what is needed. It is still too early to know. In contrast, experimental drugs to boost memory in non-Alzheimer’s age-related memory loss have shown a good deal of progress in the clinic.

With continued research, Dr. Kandel is confident the answers will be found and the right treatments developed. Our most complex organ can lead us, with enough of the right explorations, to unraveling its own mysteries of function—and dysfunction.
Despite the halting progress, so far, in developing drugs to combat memory loss in old age, there is something profoundly uplifting about the great discovery of Dr. Kandel's career, and it may be a legitimate source of hope for better results in the not-distant future.

This discovery is beautifully captured in one of Dr. Kandel's early and thought-shifting papers, notes his friend and Columbia colleague of many years, Dr. Herbert Pardes, President of the Foundation Scientific Council since its inception. “The paper was called ‘Psychotherapy and the Single Synapse’ and it deeply influenced many people, including me,” says Dr. Pardes.

Dr. Kandel explains that he set out to say two things in that paper, which appeared in the New England Journal of Medicine in 1979. “First, I pointed out that it was foolish to think that the psychoanalytic approach to mental illness and the biological approach to understanding the brain are in conflict with one another. They really support each other.

“The other point was that insofar as psychotherapy works in people, it is a learning experience. The patient and doctor work together to allow the patient, in a trusting environment, to relive earlier memories, earlier traumas and to rework them.” It's a form of learning that involves memory recall and the reworking of memory. This is highly relevant for many psychiatric illnesses, from depression to post-traumatic stress disorder.

And the optimism? It is inherent, it can be said, in the nature of the biology that makes remembering and learning possible. “I predicted, and scientists have now shown, that when psychotherapy works it’s because it produces anatomical changes, changes in the strength of synaptic connections,” says Dr. Kandel. This is his great discovery—that the tiny gaps across which adjacent nerve cells communicate are plastic; their strength changes in response to experience. When a memory is encoded, the connections at relevant synapses become stronger; when a memory is modified, the connection might become stronger or weaker.

But the arguably uplifting point is that experience routinely modifies our synapses. It is uplifting because it suggests that any given synaptic configuration is neither “given” nor “fixed as is” for as long as an organism lives. We change, our synapses change, in response to experience. It's what enables one of Dr. Kandel's dear friends, the renowned painter Chuck Close, to be one of the foremost portrait artists of our era—this, despite the remarkable fact that Mr. Close is “face-blind”—his brain is configured in such a way that it does not normally process the cues that enable us to recognize individual faces, one of the defining human attributes.

“Chuck has solved the problem,” Dr. Kandel explains. “He has learned that he doesn’t have difficulty with faces when they're flat, only when they're presented to him in three dimensions. So he makes a photograph; he lays it down and draws a grid over it; then he transfers that to canvas, piece by piece. This only begins to suggest that there are many ways around things, as a result of the creativity and plasticity of the brain.”

At the moment, science knows no way in which memory loss—whether Alzheimer's or non-Alzheimer's—can be rescued. But in the knowledge that the brain is, in biological terms, a plastic, if stupendously complicated, entity, there is more than mere hope; there is a reason based in science to believe that we can modify biological processes that lead to brain dysfunction. The possibilities for effectively treating, preventing, curing mental illness are not far-fetched illusions—with the work of scientists like Dr. Kandel evolving what we know about the brain and how it works, these goals are within our reach.
My father-in-law was treated successfully with radiation for prostate cancer 2 years ago, but ever since then he seems depressed. As is common with people in his generation, he is not open to going to therapy, nor is he even accepting he has a psychiatric issue. What can we do to help him, and do you think the depression could be caused by something physically related to his cancer treatment? Depression is often seen in the context of many medical illnesses, including cancer. The mechanisms underlying the associations are poorly understood. You should do everything you can to get your father-in-law to see someone for his depression—if not a psychiatrist, then his internist. Depression—even in the context of other illnesses—is very treatable.

I was interested in your “Behavior vs. Genetics” section in the Fall Quarterly (p. 8). Based off your mouse studies, do you think that the majority of men who are prone to stress and anxiety are fated to have children with the same issues? No. An individual’s risk for a syndrome as complex and variable as depression or anxiety is due to a large number of factors, including genetic, environmental, and presumably epigenetic. Also, depression and anxiety are not as heritable as other forms of mental illness (e.g., schizophrenia, bipolar disorder) and indeed most offspring of people with depression or anxiety avoid these syndromes. Our hope and expectation is that by better understanding the many types of disparate factors that combine to cause depression or anxiety, it will be possible to better identify those at risk and intervene to prevent the illness.

Four generations of family, possibly five, have a history that includes severe mental illness. This is not a matter of nurture as we were all raised separately. How common is this? I have chosen to not have children due to this legacy. Unfortunately, this is not uncommon, since all forms of severe mental illness are highly heritable, in particular, schizophrenia and bipolar disorder. The chances of this type of scenario likely vary a lot from family to family, since the heritability and specific genes that comprise that heritability vary.

What do you see on the horizon in the next few years as a breakthrough treatment for depression? Several rapidly acting antidepressants are currently in clinical trial, such as ketamine (see 2011 Highlights, Dr. Zarate, on p.2). These rapidly acting agents have novel mechanisms compared to currently available antidepressants and could offer significant improvement to patients who do not fully respond to today’s medications. In addition, efforts continue to identify even more antidepressant medications with novel mechanisms of action.

Is there a viral or infection component to schizophrenia that could be treated with an antiviral or an antibiotic, especially at first episode? This remains an area of active research. There is currently no definitive evidence that an antiviral agent can be of help.

Ask the Researcher

HAVE A QUESTION? You can e-mail asktheresearcher@bbrfoundation.org with questions for Dr. Eric Kandel. Select questions and answers will be published in the next issue of The Quarterly.

This column gives you an opportunity to ask questions of the researcher profiled in “Interview with a Researcher” and gives us the opportunity to bring our mission to life.

Please note that this column is intended to provide answers to questions related to scientific research and discoveries leading to better treatment of a broad range of mental illnesses. The researcher cannot give specific recommendations or advice about treatment; diagnosis and treatment are complex and highly individualized processes that require comprehensive face-to-face assessment. This Q&A forum is not meant to serve as a substitute for that, but rather to share insights.
What are the particular challenges of late-life mental health?

The challenges include deteriorating physical health, neurocognitive impairment associated with aging, financial and psychosocial stressors—and importantly, the stigma of aging. Older people with mental illness have to fight the dual stigma of aging and mental illness. They don’t have resources to advocate for themselves, and as a result, they constitute one of the most disenfranchised groups in society. Also, there is far less research on older people than on younger adults. The tendency is to transfer findings in younger adults to older ones; yet, this is inappropriate because of various psychosocial differences between the two groups as well as increasing heterogeneity with aging.¹

What is late-life depression?

According to the National Institute of Aging, if you have several of these symptoms, and they last for more than two weeks, you may be suffering from late-life depression:

- An “empty” feeling, ongoing sadness and anxiety
- Tiredness, lack of energy
- Loss of interest or pleasure in everyday activities, including sex
- Sleep problems, including trouble getting to sleep, very early morning waking and/or sleeping too much
- Eating more or less than usual
- Crying too often or too much
- Aches and pains that don’t go away when treated
- A hard time focusing, remembering or making decisions
- Feeling guilty, helpless, worthless or hopeless
- Being irritable
- Thoughts of death or suicide; a suicide attempt
The exact changes in brain chemistry and function that cause late-life depression are unknown. It is known, however, that brain changes can be triggered by the stresses of certain life events such as illness, life transitions (e.g., retirement), interpersonal conflicts, social isolation, or the death of a loved one. Up to as many as one-third of widows/widowers meet criteria for depression in the first month after the death of their spouse, and half of these individuals remain clinically depressed after one year.²

Late-onset depression may also be caused by illnesses that occur later in life (e.g., Alzheimer’s disease, Parkinson’s disease, heart disease, cancer, arthritis, diabetes), disability (especially due to stroke), or grief (such as death of a spouse). In some cases, late-onset depression might be due to small stroke-like damage to areas of the brain involved in mood regulation. Vascular risk in the elderly may increase vulnerability to depression by disrupting mood regulation circuits in the brain, decreasing its ability to respond to stressful events.³

Q Why is the suicide rate so high with the elderly population?
A Late-life depression is one of the conditions most commonly associated with suicide in older adults and is widely under-recognized and under-treated as a medical illness. Comprising only 13% of the U.S. population, individuals aged 65 and older account for 20% of all deaths by suicide. Suicide among white males aged 85 and older is nearly six times the suicide rate in the U.S. (65.3 deaths per 100,000 persons vs. 10.8 per 100,000). Studies show that many older adults who die by suicide, up to 75 percent, have visited a physician within a month before death, pointing to the urgency of improving detection and treatment of depression.²

Q Is memory loss an inevitable part of the aging process?
A For most people, occasional lapses in memory are a normal part of the aging process, not a warning sign of serious mental deterioration or the onset of dementia. The primary difference between age-related memory loss and dementia is that the former isn’t disabling. The memory lapses have little impact on daily performance and accomplishing desired tasks. When memory loss becomes so pervasive and severe that it disrupts the capacity to work, engage in hobbies and social activities or maintain supportive family relationships, this may be a warning sign of Alzheimer’s disease, or some other disorder that causes dementia or mimics the symptoms of dementia.

New discoveries are being made about the brain’s capacity to generate new cells and how it does so over the course of human life.⁴ Also, experience routinely modifies the synapses in the brain, indicating that any given synaptic configuration is neither “given” nor “fixed as is” for as long as an organism lives. We change, and our synapses change, in response to experience.⁵

Q Are there things that can be done to keep memory intact as we age?
A There is a consensus that you can do certain things to prevent non-Alzheimer’s age-related memory loss. Good health is important—staying physically fit, seeing your physicians and following their advice, keeping blood pressure under control—and if you have diabetes, getting it under control. Also by staying socially engaged and staying intellectually engaged, doing mental exercises that involve things not previously done—say, for instance, memorizing poetry—can really help as you enter old age. All of these things can act as a prophylactic for non-Alzheimer’s age-related memory loss. For Alzheimer’s, it is not at all certain that any of these things will help.⁵

Sources:
¹ Dilip V. Jeste, M.D., NARSAD Distinguished Investigator Grantee: see p. 31-32
² National Institute of Mental Health: Older Adults: Depression and Suicide Fact Sheet
³ National Institute of Mental Health: Co-occurrence of Depression With Stroke Fact Sheet
⁴ Hongjun Song, Ph.D., NARSAD Independent Investigator Grantee and colleagues: ‘New Discovery on the Brain’s Capacity to Regenerate’: see p. 2 bbrfoundation.org
⁵ Eric R. Kandel, M.D., A Nobel Laureate on Successful Aging: see p. 5-8
The Answer is Research

The Research Partnership between the Sidney R. Baer, Jr. Foundation and the Brain & Behavior Research Foundation is helping change the course of mental illness. By funding NARSAD Grants, support is given to science leading to better understanding, improved treatments and ultimately prevention and cures of mental illness.

Become a Research Partner

- Select a scientist in your area of interest, an institution or geographic area
- Develop a personal relationship with your scientist and learn more about their work through personal meetings and conversations
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For information on becoming a Research Partner or to support research in other ways, please call 1.800.829.8289 or 516.829.0091, or visit our website at bbrfoundation.org
Late-Onset Mental Illness Unravels a Family’s Life

A daughter supports mental health research to ensure other families don’t have to live through what hers did.

Among Janet Larsen’s family mementos, carefully preserved and passed down by her mother, is a letter addressed to Janet’s father, Victor Lottmann, on the occasion of his high school graduation in 1928. Written by the school’s principal, the letter extended to the young man “heartfelt congratulations on graduating with honors.” Janet gets a particular kick out of the part that says “my hope is that you keep on ascending the ladder of success until, eventually, you sit in the chair of the chief executive of this great United States.” Framed with the letter is a photo of a handsome teenager, tall and slender, the world clearly his oyster.
Although he did not become president of the United States, and despite the advent of the Great Depression, Victor Lottmann did, as hoped, climb the ladder. After earning a business degree at Washington University in his hometown of St. Louis, he went to work for what was then Ralston Purina, hired by one of the company’s founders, who was impressed by his intelligence and drive. Shortly after, in 1935, he married Edith, his childhood sweetheart. A scant dozen years later, following a stint with a management consulting firm in Chicago, he landed a senior executive post with the Ford Motor Company.

Janet, born in 1937, was followed by two younger brothers. With the move to Ford, Victor built a house for his family in Bloomfield Hills, in suburban Detroit, that seemed to his little girl “like a palace.” She recounts: “He was really moving up. He traveled a lot for the company. He gave speeches all around the country. He was smart and he was charismatic.” Most of all, as far as his adoring daughter was concerned, “he was a wonderful father.” She remembers him, in those days, “always smiling and doing fun things.” One such thing she especially remembers. “One day, out in the country, he decided it was time to teach me to drive. There I was, age 11, driving a brand new Ford.”

In those prosperous postwar days, the Lottmanns were, says Janet, the quintessential “Beaver Cleaver” clan, with an English setter named Skippy, a mother who dressed up to greet her husband each evening and a father who fixed post-movie ice cream floats for his brood, and sang with such audible enthusiasm in church that his mortified daughter “wanted to hide under the pew.”

Then, seemingly out of the blue, the loving father, dashing husband and rising young executive, age 37, stopped smiling. Janet remembers him up all night prowling the house, unable to sleep. When his performance at work began to slip, the company urged him to seek psychiatric help. He refused, insisting that there was nothing wrong with him. His symptoms worsened and he lost his job. Finally hospitalized, he was diagnosed with schizophrenia.

The beautiful home was sold and the distraught family moved back to St. Louis. For a time, the children were scattered, living with various relatives, until Edith was able to buy a small house, using the money Victor had so carefully been putting away for his children’s college education. She went to work selling real estate to support the family.

At the hospital, Victor was given electroconvulsive therapy (ECT) and eventually released. One of the few forms of treatment then available for the mentally ill, ECT technology was considerably cruder than it is now, and could have devastating effects on memory. He returned home calmed, but unable to hold a job.
“He tried working as a bookkeeper for a local company,” Janet recalls. “He lasted about a month.” The man with university training in statistics “had made too many mistakes.” Gone forever was the glamorous figure in “suit and tie, always spruced up.”

Over the next few years, except for some brief periods in a sanatorium, Victor remained, as Janet remembers him, a quiet figure sitting in front of the television set—until he “went really awry.” Following a series of violent episodes, including one in which he trashed the kitchen, Edith was advised that his condition had become too dangerous for him to remain at home. He was committed to the state psychiatric hospital in 1956, where he remained for the rest of his life, and died, in 1976, from a kidney infection at the age of 64.

With the passing of time and the advance of psychiatric research, which she tries to keep abreast of, Janet Larsen has come to believe that her father was misdiagnosed. “It seemed as if at that time everyone who had mental illness was diagnosed with schizophrenia. But he didn’t have any of the symptoms of schizophrenia.” The alternating bouts of depression and mania he experienced were, she later learned, more typical of bipolar disorder. “In those days,” she says, “most people had never even heard the term bipolar disorder.”

“Focusing on an older population with bipolar disorder is particularly important,” says NARSAD Young Investigator Grantee Brent P. Forester, MD, “given the aging of the population,” which, beyond the personal heartache to families like Janet’s, imposes an enormous socioeconomic burden.

And in those days, people kept mum. Throughout their childhood, Janet and her brothers were told almost nothing about their father’s illness. “You weren’t supposed to talk about it. There was all this pressure to keep it secret because it was so shameful.” And throughout the many years of his confinement, the family rarely visited him. The authorities at the hospital told Edith that after their visits he became extremely agitated, and it was in his best interest if they didn’t come.

In the years since, sadness at her father’s fate and at the lack of knowledge that kept him improperly treated and confined, as well as her own remorse at not having spent more time with him, have spurred Janet to become as informed and as open and forthcoming as possible with her own children about her father’s illness. She is heartened that the stigma of mental illness has lessened, that information can now be more freely exchanged, and that improvements in treatment have allowed more people like her father to live a near-normal life. As a mother of four and grandmother of 14, she is also keenly aware that mental illnesses can be passed down.

Her family’s experience, plus an acquaintance with the late Sidney R. Baer, Jr., led Janet to support the work of the Brain & Behavior Research Foundation. During several years when she was a bank trust officer, Baer
was one of her clients. The scion of founders of a department store chain, whose own life was constrained by schizophrenia, he established an organization to support mental health efforts. In 2004, the Sidney R. Baer, Jr. Foundation entered into a partnership with the Brain & Behavior Research Foundation, then called NARSAD, to help fund NARSAD Grantees. As part of that support, each year the Baer Prize, carrying a stipend of $40,000, is awarded to a NARSAD Young Investigator Grantee who has initiated innovative and promising research in schizophrenia.

Sidney Baer’s knowledge and experience of mental illness also helped to reinforce Janet’s conviction that her father’s symptoms were those of bipolar disorder, not schizophrenia. The state hospital where Victor was kept is long closed, but as a project in her retirement, Janet is hoping to track down her father’s records to learn more about the course of his illness.

Today, scores of investigators, many working with NARSAD Grants made possible by donors like Janet Larsen, are exploring the biological underpinnings of bipolar disorder, tracing its course and developing and testing new forms of treatment. Among them, Brent Forester, M.D., director of the Mood Disorders Division of the Geriatric Psychiatry Research Program at Harvard’s McLean Hospital, is one of the NARSAD Young Investigator Grantees whose work on late-life mental illness is highlighted on page 18.

Dr. Forester explains that with bipolar disorder, untreated symptoms tend to worsen with age, as may have been the case with Victor Lottmann. “Focusing on an older population with bipolar disorder is particularly important,” he says, “given the aging of the population,” which, beyond the personal heartache to families like Janet’s, imposes an enormous socio-economic burden.

Janet Larsen believes we’ve “come a long way” from the days of her father’s illness. Her hope is that with more research, once-vibrant lives will not have to end so sadly. ✤

Learn more about mental health research and the studies being funded by the Brain & Behavior Research Foundation.

Visit us at bbrfoundation.org
NARSAD Grants on Late-Life Mental Health

NARSAD Young Investigator Grantees Bring Fresh Ideas to Mental Health Research for Older Patients

As America ages, more and more young scientists are awakening to the increasingly urgent public health issue of late-life mental illness. NARSAD Young Investigator Grantees bring fresh ideas to help answer some long-standing questions, pointing the way toward improved therapies targeted specifically to the needs of older patients.

Asking such questions as: How does increasing age exacerbate treatment-resistant depression? The rate of depression can range from 55 to 81 percent in the older population. Persistent, unrelieved depression can result in severe functional disability, cognitive decline and often suicide. Elevated rates of suicide are also associated with bipolar disorder, current treatments for which are often only partially effective for geriatric patients and can have significant side effects.

For these young scientists, their research presents the possibility of helping to ease the enormous burden of mental illness on society and often requires an innovative, multidisciplinary approach to successfully treat the aging population.

Carmen Andreescu, M.D.

2009 NARSAD Young Investigator Grant: “Neural Markers of Treatment Response in Late-life Generalized Anxiety Disorder”

Objective of research: To identify biological predictors of treatment response in elderly patients with generalized anxiety disorder (GAD) to further development of personalized and effective treatments.

According to Carmen Andreescu, M.D., 2009 NARSAD Young Investigator Grantee, late-life generalized anxiety disorder (GAD) is associated with cognitive impairment and poorer recovery after events such as strokes. Its onset may reflect age-specific stressors and brain changes and she says, “late-life GAD is relatively understudied and arguably the least treated brain and behavior disorder in the elderly.”

A research assistant professor in the department of psychiatry at the University of Pittsburgh, Dr. Andreescu was trained in medicine and psychiatry in her native Romania. She completed a residency in psychiatry and a geriatric psychiatry fellowship at the University of Pittsburgh’s Western Psychiatric Institute and Clinic, before receiving her current appointment. With her NARSAD Grant, she is exploring age-related
neuroanatomical changes that may interfere with responses to treatment for GAD in the elderly, which until recently has been under-diagnosed and under-treated due to poor screening and limited awareness.

GAD is as prevalent as late-life depression, and here, too, effective treatments are lacking. Several brain areas appear to be involved in initiating and maintaining the pathological worry of GAD, particularly interactions between the amygdala and the rostral anterior cingulate, regions that, among other functions, help process emotions and the brain’s reward system. During healthy worry suppression, the rostral anterior cingulate inhibits neural output from the amygdala. Dr. Andreescu conjectures that in the elderly this mechanism might be defective due to disconnection between the two structures caused by age-related vascular changes and neurodegeneration.

Aided by structural and functional magnetic resonance imaging (MRI) technology, she is investigating amygdala-rostral anterior cingulate interaction in patients treated with selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants.

Daniel M. Blumberger, M.D.

2010 NARSAD Young Investigator Grant: “A Prospective Study of Cortical Inhibition in Treatment-Resistant Late-Life Depression”

Objective of research: To clarify the pathophysiology of late-life depression and provide early identification of treatment-resistant patients.

“I was able to help a number of older adults recover from serious depressions. The experience was extremely rewarding. I then became interested in learning more about the biology of depression in older adults and this has become a focus of my research career,” states Daniel M. Blumberger, M.D., 2010 NARSAD Young Investigator Grantee.

Dr. Blumberger is a research fellow at the University of Toronto’s Centre for Addiction and Mental Health, one of three centers involved in a National Institute of Mental Health (NIMH) study to test the efficacy of the antidepressant venlafaxine (trade name Effexor) with or without aripiprazole (Abilify) as a treatment for late-life treatment-resistant depression. With the support of his 2010 NARSAD Grant, Dr. Blumberger is using the opportunity offered by the availability of the NIMH study participants to investigate cortical inhibition, an important brain function that shows a specific pattern of disturbance in depressed patients who do not respond to antidepressant treatment.

The aging process leads to a decrease in cortical inhibition. By comparing depressed older patients and healthy controls, Dr. Blumberger wants to determine whether deficits in cortical inhibition predict treatment resistance in late-life depression. He is using a method called repetitive transcranial magnetic stimulation (rTMS) to evaluate levels of cortical inhibition. Pioneered by Brain & Behavior Research Foundation Scientific Council Member Mark S. George, M.D., rTMS is a non-invasive form of brain stimulation that probes neuronal circuits regulating mood (see 2011 Highlights, p.2).

Brent P. Forester, M.D.

2008 NARSAD Young Investigator Grant: “31P MR Spectroscopy Magnetization Transfer Study of CoEnzyme Q10 (coQ10) in Geriatric Bipolar Depression”

Objective of research: To explore the use of a novel compound, coQ10, as a treatment for older patients with bipolar disorder. CoQ10 is known to enhance cellular energy metabolism in patients with neurodegenerative disorders such as Parkinson’s disease.

The disease mechanisms of bipolar disorder remain unclear overall. Dr. Forester, director of the Mood Disorders Division of the Geriatric Psychiatry Research Program at McLean Hospital, a Harvard-affiliated psychiatric facility, and a psychiatry instructor at Harvard Medical School, is exploring abnormalities in cellular energy metabolism that have been implicated in bipolar disorder. He is testing a novel compound that may normalize aberrant energy in older patients with this disorder.
Mitochondria are the structures, or organelles, within cells that serve as the cellular powerhouse: they generate energy. Studies have shown the presence of altered energy parameters, reflecting impaired mitochondrial function, in bipolar disorder patients, but these studies have not included older bipolar patients. Dr. Forester is using magnetic resonance spectroscopy (MRS), a potent and safe technology for investigating brain biochemistry. With this technology, he is able to test the effects of coQ10 with older patients who have bipolar disorder. CoQ10 is known to enhance mitochondrial function in patients with neurodegenerative disorders such as Parkinson’s disease. To assess coQ10’s effectiveness, he will compare energy parameters and mood before and after treatment.

**Jordan F. Karp, M.D.**

2010 NARSAD Young Investigator Grant: “Buprenorphine for Late-Life Treatment-Resistant Depression”

**Objective of research:** To test the safety and efficacy of buprenorphine, a kappa opiate receptor antagonist, for treatment-resistant depression in older adults, and to translate functional magnetic resonance imaging (fMRI) results into more precise treatment planning.

I am interested in geriatric mental health “because it transcends psychiatry, psychology, medicine and cognitive neuroscience. I’m drawn to the multidisciplinary approach required to both treat and prevent psychiatric illness in late life,” says Jordan F. Karp, M.D., 2010 NARSAD Young Investigator Grantee.

Dr. Karp is an associate professor of psychiatry, anesthesiology and clinical and translational science at the Western Psychiatric Institute and Clinic of the University of Pittsburgh School of Medicine. His particular interest is in the treatment of older people with comorbid—co-existing—depression and chronic pain. His NARSAD Grant research is aimed at identifying and testing more effective medications for patients with late-life depression for whom currently available antidepressants don’t work. This treatment resistance may be complicated by other problems associated with aging, such as cerebrovascular disease or incipient Alzheimer’s disease, which may compromise brain neurocircuitry.

Based on studies suggesting that opioid drugs may exert antidepressant effects, Dr. Karp is conducting a trial to determine the potential of a compound called buprenorphine as a treatment for late-life depression. Buprenorphine acts on brain structures rich in opiate receptors, which are critical to reward circuits.

**Jian-Min Zhang, M.D., Ph.D.**

2008 NARSAD Young Investigator Grant: “Testosterone, Androgen Receptor Genotype and Late-Life Depression”

**Objective of research:** Dr. Zhang’s goal is to identify genetic markers that will determine which men will benefit from testosterone treatment for late-life depression—and which men will not and should be exempted from this treatment due to its potential side effects.

Dr. Zhang is an assistant professor of psychiatry and director of the Geriatric Psychiatry Division at the University of Maryland in Baltimore, and directs the geriatric psychiatry service at the University of Maryland Medical Center. In his NARSAD Grant-supported project, begun in 2008, he has focused on depression in the elderly male population.

Hypogonadism—a deficiency in the hormone testosterone—affects 30 percent of men over the age of 55. Hypogonadal men are three times more likely to suffer from depression and are more likely to become treatment resistant. Testosterone as a treatment for hypogonadism has had mixed results, which may reflect lack of attention to the functional status of androgen receptors (AR), the cellular receptors for testosterone, which must be working properly for testosterone to have the appropriate effects in the body and the brain.

Dr. Zhang is studying differences in AR genes among elderly men to see whether these differences are associated with response to testosterone. His goal is to determine whether AR receptor gene types can be used as genetic markers for men who will benefit from testosterone treatment and exempt those who would not, since testosterone therapy carries a potential increased risk for prostate cancer.
Caring for loved ones with special-needs can be an expensive commitment ranging from medical care to housing needs. Planning for the day that a caregiver is no longer around, or addressing the financial limitations of caregivers, are two reasons to consider this type of trust.

What is a Special-Needs Trust?
A Special-Needs or Supplemental Trust, is a way to secure assets for your loved one that ensures access and availability to money for them. Establishing a Special-Needs Trust also guarantees that your loved one will continue to qualify for government-assistance programs and support. Often times, direct support of a loved one can eliminate qualifying for government assistance programs.

How does a Special-Needs Trust and government program support work?
Loved ones with special needs resulting from a mental illness qualify for government assistance programs such as Medicaid. Most times, Medicaid covers medical services and housing, along with Supplemental Social Security Income. This aid, however, is often income restricted. Depending on your state’s income threshold, gifts to your loved one might disqualify them from government programs.

How do I set up a Special-Needs Trust?
Only your legal advisor can assist you with establishing a Special-Needs Trust as rules vary from state to state.

How can I fund the trust?
Once the legal document is established, you can fund your trust throughout your lifetime. Alerting family to the establishment of the trust is also a good idea as an inheritance directly to your loved one might disqualify them for government programs and services. Gifts should be made to the trust and not to your loved one.

How will my loved one benefit from the trust?
As trustee, or someone you designate to serve in this role, the trust funds can be used immediately to help your loved one. While they might benefit from government programs that assist with medical care and housing, for example, the trust would be used for enhanced care that improves the quality of life—ranging from gym memberships to alternative medical care.

To learn more about ways in which you and a loved one can benefit from a Special-Needs Trust, or to find out ways to support the work of the Brain & Behavior Research Foundation, please call (516) 829-0091.

bbrfoundation.org
Glossary

Helpful definitions of terms used in this issue.

**Psychosis** (page 3): A loss of contact with reality, usually including false beliefs about what is taking place or who one is (delusions) and seeing or hearing things that aren’t there (hallucinations). Recent research suggests that psychosis might become a distinct psychiatric diagnosis that has separate risk factors and might also require separate treatments (visit our blog entry featuring Dr. Elena Ivleva, 2010 NARSAD Young Investigator Grantee to learn more: http://bbrfoundation.org/blog).

**Support Vector Machine (SVM)** (page 3): A machine that enables an innovative technique to evaluate magnetic resonance imaging (MRI) data and recognize patterns in the neuroanatomy of the brain.


**Gene Expression** (page 4): The process by which information from a gene is used in the synthesis of functional gene products; i.e., the proteins that perform the specific functions of a cell.

**Messenger RNA, or mRNA** (page 5): Molecules that transcribe the information in DNA that is carried to centers in a cell where the proteins that perform life's functions are produced. This process is called “transcription.”

**mRNA transcripts** (page 4): The transcribed messages that are carried by mRNA (see above).

**Transcriptome** (page 4): A set of mRNA transcripts (see above) that constitute an individual’s molecular signature.

**Prefrontal cortex** (page 4): The region in the brain responsible for higher cognitive functioning, such as planning and judgment.

**Generalized Anxiety Disorder, or GAD** (page 18): An anxiety disorder that is characterized by excessive, uncontrollable and often irrational worry about everyday things that is disproportionate to the actual source of concern.

**Rostral Anterior Cingulate** (page 19): A region in the brain that, among other functions, helps process emotions and the brain’s reward system.

**Repetitive Transcranial Magnetic Stimulation (rTMS)** (page 19): A noninvasive brain stimulation technology for examining neuronal circuits that regulate mood in the treatment of depressed patients who have been resistant to other forms of treatment. Developed by Mark S. George, M.D., (see 2011 Highlights, p.2) Brain & Behavior Research Foundation Scientific Council Member, with the support of an initial NARSAD Young Investigator Grant as an alternative for electroconvulsive therapy (ECT) in treatment-resistant depression. The FDA approved this treatment in 2008.

**Opioid drugs** (page 19): An opioid is any agent that binds to opioid receptors, found principally in the central nervous system and gastrointestinal tract. Examples include morphine, codeine, oxycodone and heroin.

**Electroconvulsive Therapy (ECT)** (page 14): Formerly known as electroshock, ECT is a psychiatric treatment in which seizures are electrically induced in anesthetized patients for therapeutic effect in the treatment of mood disorders such as depression and bipolar disorder.
As research breakthroughs continue to be made, new treatments and therapies for people living with mental illness point toward recovery.

THREE STEPS TO MENTAL HEALTH

Step 1: DISCOVERY
Understanding malfunctions in the brain

Step 2: TREATMENT
Reducing symptoms and retraining the brain

Step 3: RECOVERY
Supporting rehabilitation to enable full, productive lives
Addressing Sleep Problems in Schizophrenia Patients Serves New Role in Therapy
Schizophrenia patients often have difficulty sleeping, experiencing frequent disturbances in their sleep patterns throughout the night. However, doctors do not always take into consideration how much sleep problems can affect mood, social function, mental abilities and quality of life. Findings from recent studies at the University of Oxford has the research team there urging clinicians to either treat their patients’ sleep problems or refer them to sleep specialists. The study compared 20 schizophrenia patients who were stabilized on their medications to a group of 21 healthy controls. Despite the schizophrenia patients’ stabilized mood and drug regime, they all took longer to fall asleep, slept longer and at more erratic times, spent more time in bed and had more disruptive patterns than the healthy group. The sleep issues create a state of constant jetlag, suggesting inherent body clock issues to be further investigated. Including sleep therapy to the course of treatment for schizophrenia patients may greatly improve quality of life.
Source: British Journal of Psychiatry

Can a Derivative of a Curry Spice Help Prevent Progression of Alzheimer’s Disease?
Alzheimer’s disease slowly robs a person of memory and cognitive faculties, and up until now, there have been no cures or treatments for the terminal illness. However, researchers at the Salk Institute for Biological Studies have high hopes for a new drug they have developed that has been shown to halt the progression of memory loss and prevent brain damage, which would make it a prime candidate for Alzheimer's treatment in the near future. The team tested the drug they call J147—which is derived in part from curcumin, a curry spice—as an oral medication in mice with normal neurological function, resulting in improved memory function. Next, the team tested the drug in mice with Alzheimer’s and the results indicated that the mice and rats increased the production of a brain protein involved in memory function called brain-derived neurotrophic factor (BDNF). The rats and mice also showed improvement in memory function. The team concluded that the drug J147 could be tested soon on humans with Alzheimer’s, leading the way to a first-ever treatment for the disease.
Source: PLoS ONE Journal

Omega-3 Supplements Used as Treatment for Depression in Elderly
Recent studies at King’s College London and National Institutes of Health have indicated a direct connection between diet and depression and anxiety in older people. The studies were conducted on 130 participants, aged 60 to 86 years of age, and found that deficiencies and imbalances in the omega fatty acids had a connection to mood and anxiety.

Essential fatty acids Omega-3 and Omega-6 can only be obtained through diet—Omega-6 is found in most foods, however, Omega-3 is found only in leafy green vegetables and cold-water fishes. Because Omega-3 is often scarce in Western diets, Omega-6 is naturally substituted, which can result in depression and anxiety, according to the King’s College research. The FDA has yet to evaluate these findings, however the research suggests new treatment directions with dietary supplementation.
Source: Journal of Affective Disorders, National Institutes of Health
**JANUARY**

**January 7 & 8, Orlando, Florida**  
Walt Disney World Half & Full Marathon  
**Team Daniel**  
Members of the Laitman family will be running in the Half-Marathon on January 7 and the Full-Marathon on January 8. Visit the Team Daniel web page and see where they will be next. [bbrfoundation.org/events/TeamDaniel](http://bbrfoundation.org/events/TeamDaniel)

**FEBRUARY**

**Ongoing, Chatsworth, California**  
**Brain-Sells**  
Justin Miller will continue to recycle aluminum, plastic, glass, old cell phones, jewelry and more. Based in Chatsworth, California, to find out how you can join Justin's team or send your recyclables to him go to [bbrfoundation.org/events/Brain-Sells](http://bbrfoundation.org/events/Brain-Sells)

**Ongoing, Manhasset, New York**  
**Neil's Wheels**  
Neil, his father Greg and members of the community help feed the homeless—many who suffer from mental illness. They direct all funds raised to the Brain & Behavior Research Foundation with the hope that Neil will benefit from improved treatment, advances and breakthroughs. Find out how you can join Neil’s team by visiting [bbrfoundation.org/events/neilswheels](http://bbrfoundation.org/events/neilswheels)

**February 9, Newport Coast, California**  
**The Teenage Mind: What Every Parent Needs to Know**  
Brain & Behavior Research Foundation-funded NARSAD Grantees will discuss their work on the “teenage mind” and explore issues as diverse as depression, sleep, mood and substance abuse. Taking place at the Sage Hill School
SAVE THE DATES!
2012 Upcoming Events

The Teenage Mind: What Every Parent Needs to Know
February 9, 2012
Sage Hill School
Newport Coast, California

Klerman-Freedman Awards Dinner
July 27, 2012
Le Parker Meridien
New York City, New York

Women’s Mental Health Conference: The Art and Science of Caring
September 14, 2012
New York City, New York

Annual New York City Mental Health Research Symposium
October 26, 2012
Bohemian National Hall
New York City, New York

Annual National Awards Dinner
October 26, 2012
The Pierre
New York City, New York

Visit our website for information about upcoming webinars and TeamUp! Events

bbrfoundation.org/events
Our Campaign Objective:
Accelerate the breakthroughs with $200 million in new support over five years

What will $200 million achieve?

• $120 million additional funding for Young Investigators
  o Increase grant amount from $60,000 to $90,000 over two years
  o Grants awarded to the most promising young scientists

• $50 million additional funding for Independent Investigators
  o Grants awarded to researchers during critical period between initiation of research and receipt of sustained funding

• $30 million additional funding for Distinguished Investigators
  o Grants used to fund a particularly talented, established investigator

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• Planned Giving
• Family Foundations
• Foundation Giving
• Sponsor a “Named” Lecture or Webinar
• TeamUp!

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…Climbs Mountains

Climbing-4-PTSD, Grand Rapids, Michigan

…Walks for Miles

Taking Strides Against Mental Illness
Ridgewood, New Jersey

…Tees Off

Chrissy’s Wish Memorial Golf Outing
Manorville, New York

…Recycles

Brain-Sells, Chatsworth, California
(read their blog entry at bbrfoundation.org/blog)

How will you support our cause?

Find out how you can TeamUp! and fund research that will lead to advances and breakthroughs. Remember—100% of all donor contributions for research are invested in NARSAD Grants.

Visit bbrfoundation.org/TeamUp or call Special Events: 800.829.8289, 516.829.0091
Depression and Dementia: Which Comes First?
Deborah E. Barnes, Ph.D., M.P.H.

Cognitive abilities tend to decline with age. Although there is considerable variability in degree from one person to another, a large percentage of the very old develop dementia. By contrast, depression is not a normal part of aging, but many of the problems of aging—bereavement, illness, social isolation—can be risk factors for depression and affect cognitive abilities.

Depression is very prevalent in people with dementia, with estimates ranging as high as 50 percent. Depression combined with chronic stress can damage the brain. Some studies have shown that people with depression have a smaller than normal hippocampus, a brain structure associated with learning and memory.

One of the questions researchers are addressing is which comes first: Does dementia trigger depression or vice versa? It may be that depression is an early symptom of dementia; or that changes in the brain causing dementia in turn cause mood changes. Or it may be that depression causes a lower threshold in susceptible people. It is even possible that some people have a genetic factor that increases the risk for both depression and dementia.

Studies by scientists suggest that depression comes first and may be a risk factor for dementia. Researchers have been studying data from more than 13,000 long-time members of the Kaiser medical plan, looking at mid-life versus late-life depression as dementia risk. They have found that people with mid-life depression that abated before old age did not show an abnormal rate of dementia in old age. Those with depression that arose late in life, however, had twice the average risk for Alzheimer’s disease and a 50 percent increased risk for vascular dementia, which is dementia caused by impaired blood circulation in the brain, a possible result of a stroke.

Another important question is what treatments are available and how effective are they? A trial in which people with depression were treated with selective serotonin reuptake inhibitor (SSRI) antidepressants, including fluoxetine (Prozac) or sertraline (Zoloft), showed improved if not completely normalized cognitive function. But whether or not treatment can delay the onset of dementia is unknown. The drugs currently available for dementia...
are not very effective. A number of drugs are under study currently, including drugs with different mechanisms of action. The goal is to provide longer, better relief or, ideally, to prevent the onset of dementia.

Can Quitting Smoking Increase Longevity for the Mentally Ill?: An Innovative Approach
Mary F. Brunette, M.D.

People with mental illness tend to smoke more than the general population. One reason that has been suggested is the self-medication effect. Research has demonstrated that if you put nicotine patches on the arms of normal non-smokers, they will show improved attention and memory and respond more to rewarding stimuli, behaviors that are impaired in people with severe mental illnesses such as schizophrenia. However, smoking is one of the factors contributing to the high rate of early death among people with mental illness: on average 25 years earlier than the general population.

Research on smoking cessation treatments in the general population has shown that nicotine replacement increases the ability to quit by a factor of one and a half, and that high-dose nicotine replacement doubles the odds. Medicine combined with behavioral therapy improves the prospects even further. A growing body of literature suggests that these methods also work among people with mental illness, but there are limited funds to support smoking cessation programs. Dr. Brunette and her colleagues are working to implement programs that help to motivate and assist smoking cessation in this population in a cost-effective way.

Decision-support systems are systems that provide concrete, comprehensible information and motivational material, often provided electronically, making it possible to provide a lot of information rapidly and cheaply and tailored for a particular population. Dr. Brunette and her team have developed a simple program designed specifically for people with severe mental illness who have cognitive deficits and may have difficulty navigating typical websites. Her site provides information and simple exercises that allow users to insert their own ideas and information and get feedback. Properly set up, the program requires no ongoing clinician time, which should make it attractive for public mental health systems with limited funds.

Initial testing of the program with people with mental illness who have little past experience with computers has had positive results. Within two months of initiating the program, 70 percent of the participants had met with a treatment provider or initiated efforts to quit smoking. The Brunette team is now expanding the program and designing sites specifically for African-American and Latino participants.
OCD: Identifying What Works Differently in the Brain and If It Can Be Remedied Over Time

Kate D. Fitzgerald, M.D.

Obsessive-compulsive disorder (OCD), the most severe of the anxiety disorders, is characterized by recurrent, intrusive thoughts or obsessions—irrational fears of danger, illness or germs, for example—and repetitive, ritualistic behaviors and compulsions, such as constant hand washing. The symptoms of OCD generally begin manifesting in childhood or adolescence, suggesting that there may be something abnormal occurring during the brain’s development.

The posterior medial frontal cortex (PMFC) and the ventral medial frontal cortex (VMFC) are regions of the brain that have been found to be hyperactive in people with OCD. In tests that Dr. Fitzgerald and her team conducted with OCD children and normal controls performing cognitive tasks, the OCD children performed correctly, but imaging studies showed that their brains had to work harder to filter out distracting information to get the correct response—they had too much activity in both regions. In the resting state, the PMFC was insufficiently connected to a posterior part of the brain important for task control. For both filtering out distracting information and responding to errors, the VMFC was activated in the OCD children, when it should have been turning off. The VMFC, too, was abnormally connected within brain networks.

A next step will be to study larger numbers of children with OCD at each age, following them to see how their brains change over time. This is especially important because recent studies suggest that OCD may, in some cases, remit. With good treatment, in particular cognitive behavioral therapy (CBT), with or without medications, up to 40 or 50 percent of OCD children get better. A particularly effective form of CBT for OCD is what is known as exposure and response prevention. There are also good medications, but many people have to go through three or four different drugs to find one that works for them.

What is not known as yet is how to predict which people will get better. If it becomes possible to characterize the brain, and how development may be going awry in the particular regions or networks of brain regions to give rise to OCD, it may be possible to use imaging tools to predict who is at risk for developing the disorder and to come up with early interventions and possibly preventative measures.
Meet A Distinguished Investigator

Dilip V. Jeste, M.D.
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2002 NARSAD Distinguished Investigator Grantee

What made you enter the psychiatric field, and why do you particularly focus on late-life mental health issues?
As a teenager growing up in India, I was fascinated by Freud’s books regarding interpretation of dreams and everyday errors of life. I felt that these books were similar to detective stories and murder mysteries—except that they sought to uncover secrets of the mind. I decided to go to medical school in order to become a psychiatrist—which was considered, to put it mildly, “a very unusual choice” by others. My goal was to study the science of the mind.

My interest in aging began much later and was driven by the fact that the population of the world is aging. The number of people over 65 in the U.S. will double in the next two decades. I also found on reading the relevant literature that the numbers of older people with mental illness will rise even faster than those in the general population. Therefore, this seemed like an exciting area for new studies.

What are the particular challenges of late-life mental health?
The challenges include deteriorating physical health, neurocognitive impairment associated with aging, financial and psychosocial stressors—and importantly, the stigma of aging. Older people with mental illness have to fight the dual stigma of aging and mental illness. They don’t have resources to advocate for themselves, and as a result, they constitute one of the most disenfranchised groups in society. Also, there is far less research on older people than on younger adults. The tendency is to transfer findings in younger adults to older ones; yet, this is inappropriate because of various psychobiosocial differences between the two groups as well as increasing heterogeneity with aging.

You have done extensive research on late-life psychosis and its treatment. What are the particular challenges in this area and how is it different from other psychosis (early-onset or other)?
Late-life psychosis includes late-onset psychosis as well as persistence (or recurrence) of psychosis that first manifested earlier in life. The amount of published research on psychosis in late life is miniscule compared to that in younger people. Whereas schizophrenia and bipolar disorder are the two most important causes of psychosis earlier in life, the etiology becomes more complex and varied in later life. For example, psychosis associated with Alzheimer’s disease and other dementias is more or less restricted to older adults. The number of people with psychosis associated with dementia is comparable to the number of people with schizophrenia across all age groups.

There is an interesting gender difference between early-onset and late-onset schizophrenia. Whereas males with schizophrenia markedly outnumber their female counterparts until about 30 years of age, the gender proportions
reverse after age 45, possibly hinting at a role of hormones such as estrogens in late-onset schizophrenia.

You are a widely recognized expert in the field of geriatric mental illness and received a NARSAD Distinguished Investigator Grant. What did the NARSAD Grant enable you to do?

My younger colleague Elizabeth Twamley, Ph.D., and I initiated a study of work on rehabilitation in middle-aged and older adults with schizophrenia. The conventional wisdom is that persons with schizophrenia, especially the older ones, would be incapable of gainful employment. Yet, we found that, with appropriate support and guidance, many middle-aged and older people with schizophrenia not only could be employed, but they stayed on the jobs, and had an improvement in their functioning as well as quality of life. The critical element in making this possible was societal support.

Please highlight the discovery you have made that you are most proud of and tell us why.

In recent years, I have been working on successful psychosocial aging. I have found that, even in people with serious mental illnesses such as schizophrenia, the functioning improves with age. People who have suffered from a mental illness for decades learn from their experience slowly but surely. Many of them develop insight, begin to differentiate psychopathology (delusions, hallucinations) from normal experience, become more adherent to their treatment in order to avoid relapses, stop using substances of abuse and become happier. While some of this may be due to survivor cohort effect (i.e., the sickest individuals die young and do not live into older age), that is not the whole story. We have been following people with schizophrenia for the past 25 years, and have commonly noticed progressive improvement of this type. Whether one may call it recovery or sustained remission, the improvement with aging is often remarkable. With better treatments and greater social support, this should become a norm.

What is the most important question you would like to answer about the aging brain and late-life mental health?

While most people associate aging with degeneration, deterioration, disability, disease, and then death, I am fascinated by psychoneuroplasticity of aging. Aging is often associated with increasing wisdom through better social decision making. The most important questions for me relate to the underlying neurobiology and the behavioral and environmental factors that promote the neuroplasticity of aging.

What else would you like to say about late-life mental health?

Older people (with or without mental illness) are an invaluable resource for the society in terms of their wealth of experience and wisdom. It is unfortunate that they are usually considered a drain on the society. The more we learn about regeneration of an aging brain and about how to promote and use the resulting wisdom, the better the society will be.
Helen S. Mayberg, M.D., NARSAD Grant recipient in 1991, 1995 and 2002

How I turned a $60,000 NARSAD Grant into more than $8.5 million worth of additional depression research funding

Helen S. Mayberg, M.D., NARSAD Grant recipient in 1991, 1995 and 2002

To learn more about how you can invest in the most promising brain and behavior research like that of Dr. Mayberg's, please call us at (516) 829-0091 or visit our website at bbrfoundation.org.
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