BRAIN & BEHAVIOR RESEARCH FOUNDATION

15 Published Research Findings in 2015

Listed In Order of Occurrence

1

Vince D. Calhoun, Ph.D.
The Mind Research Network

2004 NARSAD
Young Investigator Grant

Basic Research: Addiction

Long-Term Effects of Marijuana on the Brain**

Studies of the long-term effects of marijuana on the brain have provided an inconsistent picture, in part due to variations in research methods. In a study using a wide range of brain-scanning methods to characterize brain alterations associated with chronic marijuana use in 48 marijuana users and 62 matched control subjects, Dr. Calhoun and colleagues found changes in gray matter volume and potential functional abnormalities in grey matter as well in connections within the brain's white matter. Specifically, they found that chronic exposure to marijuana reduces gray matter volume in the orbitofrontal cortex; increases structural and functional connectivity; and leads to neural alterations that are affected by the age of onset and duration of use. All in all, these findings suggest that chronic marijuana use results in complex neuroadaptive processes. Future studies will be needed to determine whether these changes revert back to normal following prolonged abstinence.

Journal: *Proceedings of the National Academy of Sciences*, November 25, 2014

2

Tobias Gerhard, Ph.D.
Rutgers University

2010 NARSAD
Young Investigator Grant

*Team included:
Davangere P. Devanand, M.D., 1997 Independent Investigator, 1987 Young Investigator and Mark Olfson, M.D., M.P.H., 2005 Distinguished Investigator

Basic Research/Treatment: Bipolar Disorder

Lithium Linked to Lower Incidence of Dementia in Older People with Bipolar Disorder

Analyzing data from 40,000+ adults with bipolar disorder, the team* found that regular treatment with lithium correlated with lowered risk of dementia in patients over 50. For those who took lithium more than 300 days during the year prior to taking part in the study, dementia developed over the study period of three years less frequently than for those who took the drug less frequently or not at all during the same period. Using lithium sporadically or intermittently did not affect the incidence of dementia, nor did treatment with anticonvulsants, no matter how often they were used. Patients with bipolar disorder are thought to be more likely to develop dementia than people without the disorder. The new study contributes to the evidence that consistent treatment with lithium—and not anticonvulsants—may reduce this risk.

Journal: *British Journal of Psychiatry,* January 22, 2015

3

J. John Mann, M.D.
Columbia University

Scientific Council Member

2008 NARSAD
Distinguished Investigator
Grant

*Team included:
2001 Distinguished Investigator
David A. Brent, M.D.,
1998 and 1996
Young Investigator
John G. Keilp, Ph.D.,
and 2013, 2004
Young Investigator
Nadine M. Melhem, Ph.D.

Prevention/Diagnosis: Suicidal Behavior

Parent's History of Suicide Attempts Helps Predict Suicide Attempts In Children

After six years of following 701 children of 334 people diagnosed with a mood disorder, Dr. Mann's team* concluded that three long-term risk factors are most useful in predicting suicide attempts: a family history of suicide attempts, a family history of mood disorders, and a personal history of impulsive aggression. It's important that such families focus on early detection and treatment of mood disorders and aggressive-impulsive traits, the team advised. Having a parent who had attempted suicide made it nearly five times more likely that one of their children would make an attempt.

Journal: *JAMA Psychiatry*, February 2015

4

Helen Lavretsky, M.D.
Semel Institute, University of California, Los Angeles

1999 NARSAD
Young Investigator Grant

Next-Generation Treatments: Depression (Geriatric)

Combined Drug Treatment Improved Results in Geriatric Depression**

Dr. Lavretsky and her team reported results of the first comprehensive and well-controlled trial to find out if the drug methylphenidate (Ritalin) can enhance clinical and cognitive outcomes in patients with geriatric depression. Combination treatment over 16 weeks with citalopram (Celexa) and methylphenidate did in fact result in higher remission rates (62% vs. 42%) and shorter time to remission than treatment with citalopram alone. The rate of side effects was the same in both treatment modes. Citalopram treatment appeared to be beneficial for cognition, although augmentation with methylphenidate did not offer additional benefits. However, participants treated with methylphenidate demonstrated improvement in their global cognitive performance score. Improvements were also noted in clinical reports of "wellbeing" in the group that received combined treatment.

Journal: *American Journal of Psychiatry,* February 13, 2015

5

Mark H. Rapaport, M.D.
Emory University School of Medicine

1999 NARSAD Independent Investigator Grant

Andrew A. Nierenberg, M.D.
Massachusetts General Hospital

Scientific Council Member

2013 Foundation Colvin Prizewinner and NARSAD Distinguished Investigator Grant 2003, 2000 NARSAD Independent Investigator Grant

David Mischoulon, M.D., Ph.D.,
Massachusetts General Hospital

2000, 1998 NARSAD Young Investigator Grant

Next-Generation Therapy: Depression

Omega-3 Relieves Depression Symptoms in People With Bodily Inflammation

Research demonstrated that certain fatty acids, including omega-3, can reduce symptoms of depression in people with high levels of inflammation in their body. The study focused on omega-3 fatty acids. People with major depressive disorder were given one of two types of omega-3s, called EPA and DHA. People with high inflammation showed a greater reduction in depressive symptoms if taking EPA, relative to people taking placebos. People without elevated inflammation responded less to EPA than either DHA or placebo. The different effects may stem from EPA's stimulation of anti-inflammatory chemicals in the body—chemicals that DHA does not stimulate.

Journal: *Molecular Psychiatry*, March 24, 2015

6

Cynthia S. Weickert, Ph.D.
University of New South Wales, Australia

2004 NARSAD Independent Investigator Grant

2001, 1999 NARSAD Young Investigator Grant

*Team included: Young Investigators Rhoshel K. Lenroot, M.D., (2003) and Ans Vercammen, Ph.D., (2010) along with Independent Investigator grantee Jayashri Kulkarni, MBBS, MPM, FRANZCP, Ph.D., (2000), and her husband and first author Thomas W. Weickert, Ph.D.

Next-Generation Therapy: Schizophrenia

Estrogen Drug Improves Cognition in Schizophrenia Patients

Dr. Weickert's team* discovered the estrogen-related drug raloxifene can help improve some cognitive problems in schizophrenia that are hard to treat with existing drugs. Estrogen is a protector of nerve cells in the brain. The team found estrogen receptors are altered in some people with schizophrenia, blunting their ability to respond to the hormone's beneficial effects. Raloxifene, used to treat osteoporosis in women, stimulates estrogen receptors and can help overcome a blunted estrogen response. Examining the responses of 98 patients, both male and female, the team found those taking 20 mg of oral raloxifene daily for six weeks in addition to their usual antipsychotic had improved scores on memory and attention tests, compared to those taking placebo plus antispychotic. The drug didn't reduce the severity of schizophrenia symptoms compared with placebo, but it did reduce the number of symptoms experienced overall, and its effects continued after withdrawal of the drug.

Journal: *Molecular Psychiatry*, May 18, 2015

7

Patrick F. Sullivan, M.D., FRANZCP
University of North Carolina School of Medicine and the *Karolinska Institute*

2014 Lieber Prizewinner

2010 NARSAD Distinguished Investigator Grant

Dorret I. Boomsma, Ph.D.
VU University Amsterdam, Netherlands

2011 NARSAD Distinguished Investigator Grant

Basic Research: Depression/MDD

Gene Expression Analysis Points Toward Pathways Involved in Major Depression

An international team identified 119 genes whose activity differs significantly in people with major depressive disorder. Whether stemming from inherited genetic factors and/or environmental influences, these gene expression changes help point scientists toward biological pathways likely to be involved in the disorder. Many of the 119 genes whose activity differed in depression were related to immune system function. The study also pointed to 19 genes whose expression was more likely to have returned to normal if an individual had recovered from an earlier depression.

Journal: *Molecular Psychiatry*, May 26, 2015

8

Sohee Park, Ph.D.
Vanderbilt University

2012 NARSAD Distinguished Investigator Grant

2004 NARSAD Independent Investigator Grant

1996, 1991 NARSAD Young Investigator Grant

Next-Generation Therapy: Schizophrenia

Non-Invasive Stimulation Reworks Brain Waves, Improves Cognition

Dr. Park's team discovered that transcranial direct current stimulation (tDCS), a non-invasive, affordable and portable way to stimulate the brain, can help induce normal neural activity and make thought processes more flexible in people with schizophrenia. The method, which stimulates the brain at low current via electrodes placed on the scalp, is a drug-free and safe way of treating debilitating cognitive problems in schizophrenia, for which antipsychotics are not completely effective. After a 20-minute treatment, key brain waves were observed in patients to "normalize" by showing greater synchrony, in this way more resembling patterns seen in healthy controls.

Journal: *Proceedings of the National Academy of Sciences*, June 29, 2015

9

Marc G. Caron, Ph.D.
Duke University

Scientific Council Member

2013 Lieber Prizewinner

2005 NARSAD Distinguished Investigator Grant

Next-Generation Therapy: Schizophrenia

New Compounds Show Promise in Treating Schizophrenia Symptoms

Two new small-molecule drugs tested in mice alleviated some symptoms of schizophrenia-like behaviors, including movement abnormalities, social avoidance, and cognitive performance. Current antipsychotic drugs bind to and block one specific communication pathway through dopamine D2 receptors on nerve cells, but the receptors are involved in other signaling pathways. The team found that drugs called UNC9975 and UNC9994 influence the beta-arrestin communication pathway and reduced hyperactive movements, improved memory for novel stimuli, and made the test mice more social. The work shows that hitting other pathways in schizophrenia has the potential to treat symptoms in more individualized, fine-tuned ways.

Journal: *Neuropsychopharmacology,* July 1, 2015

10

Kerry J. Ressler, M.D., Ph.D.
McLean Hospital, Harvard Medical School

Scientific Council Member

2005, 2002 NARSAD Young Investigator Grant

Next-Generation Therapy: Anxiety, Post-Traumatic Stress Disorder

Drug Helps Mice Respond Normally to Fear After Traumatic Experience

Dr. Ressler and colleagues demonstrated that treatment with the corticosteroid drug dexamethasone can help mice overcome a pre-conditioned trauma-related fear response. They trained a group of mice using sounds and mild electrical shocks to learn and then to inhibit a specific fear. Animals that had experienced a traumatic event before the fear training were more likely to inhibit or extinguish the fear if they were given a low dose of dexamethasone four hours beforehand to suppress the internal stress response. The fear was also more likely to remain extinguished 24 hours later in those same animals, suggesting the potential of this approach in development of new therapeutics to treat PTSD and anxiety.

Journal: *Neuropsychopharmacology,* July 15, 2015

11

Flora M. Vaccarino, M.D., Ph.D.
Yale University

2011 NARSAD Distinguished Investigator Grant

2003, 2000, 1993, 1990 NARSAD Young Investigator Grant

Next-Generation Technology/Basic Research: Autism

Watching Patient-Derived Brain Cells Take Shape in the Lab Reveals Autism Defect

By reprogramming skin cells sampled from autistic people to grow into brain-like clusters of cells called organoids, Dr. Vaccarino and colleagues* uncovered a developmental flaw that seems to skew the balance of excitatory and inhibitory neurons in the brain. The findings suggest that overproduction of certain cell types during early development could lead to faulty brain wiring in people who later display symptoms of autism and ASD. The team correlated overactivity of a gene called FOXG1 to overproliferation of neurons; in organoids in which this gene was blocked, key developmental defects did not appear, pointing to FOXG1 activity as a potential diagnostic marker and treatment target in autism.

Journal: *Cell*, July 16, 2015

*2013 Young Investigator Gianfilippo Coppola, Ph.D. was also a member of the scientific team.

12

Patrick McGorry, M.D., Ph.D., FRCP, FRANZCP
University of Melbourne, Australia

2015 Lieber Prizewinner

1998 NARSAD Distinguished Investigator Grant

Next-Generation Treatments: Psychosis, Schizophrenia, Bipolar Disorder

Omega-3 Supplements Linked to Reduced Risk of Developing Psychosis**

Dr. McGorry, along with study leader Dr. G. Paul Amminger and colleagues, found that a 12-week course of omega-3 polyunsaturated fatty acid (PUFA) supplements reduced the risk years later that young adults would develop schizophrenia or other psychiatric illnesses such as major depression or bipolar disorder. The team's prior study showed benefits extending up to a year after a 12-week treatment course. The new study looked at the longer-term impact of the supplements among 81 people aged 13 to 25 with early symptoms of psychosis. After following the patients for an average of 6.7 years after treatment, four of 41 patients (9.8%) who received the omega-3 PUFAs had at some point developed a psychotic disorder, compared to 16 of 40 (40%) of those who received placebos. It's not clear exactly how omega-3 PUFA affects the development of psychosis. It has been postulated to reduce inflammation in the brain and aid the growth of new neurons.

Journal: *Nature Communications*, August 11, 2015

13

Next-Generation Diagnostic/ Treatment: Depression/MDD

Size of Brain Structure May Predict Effectiveness of Ketamine

Chadi Abdallah, M.D.
Yale University

2015 Klerman Prize Honorable Mention

2014, 2012 NARSAD Young Investigator Grant

*Including: Sanjay Mathew, M.D., 2009 Independent Investigator, 2006, 2001 Young Investigator and Ramiro Salas, Ph.D. 2012 Young Investigator

People with severe depression often have smaller-than-normal hippocampi—twin brain structures involved in memory and learning. Such people often respond poorly to traditional antidepressants. Dr. Abdallah and colleagues* used MRI scans to assess the size of the hippocampus in 13 patients with major depression, and then gave each patient a single dose of ketamine. For 10 individuals, symptoms of depression were reduced within 24 hours. Those who responded best were those with the smallest hippocampi on the brain's left side. For scientists who hope to use ketamine to treat treatment-resistant depression, it's another important piece in the puzzle of understanding which patients might benefit the most.

Journal: *Journal of Pyschopharmacology*, August 13, 2015

** *New England Journal of Medicine's Journal Watch Psychiatry Top Stories of 2015*

14

Avshalom Caspi, Ph.D.
Duke University

2010 Ruane Prizewinner

Terrie E. Moffitt, Ph.D.
Duke University

2010 Ruane Prizewinner

Guilherme V. Polanczyk, M.D., Ph.D.
University of São Paulo School of Medicine, Brazil

2008 NARSAD Young Investigator

Basic Research/Next-Generation Diagnosis: ADHD

Distinguishing Childhood and Adult Forms of ADHD**

New research led to unexpected insights about attention deficit-hyperactivity disorder (ADHD). The team followed a single group of over 1,000 individuals born between 1972 and 1973 in Dunedin, New Zealand, 95 percent of whom were still taking part in the study at age 38. Participants were comprehensively examined at a dozen intervals over the years. During childhood, six percent of the group, mostly boys, were diagnosed with ADHD. But in adulthood, only three percent received an ADHD diagnosis, with males and females affected about equally. The great surprise was that almost none of those with adult ADHD were among the portion of the group that had been diagnosed during childhood. The study raises the possibility that adult ADHD is not a neurodevelopmental disorder that begins in childhood, as is widely believed, but may in fact be a separate condition with other causes.

Journal: *American Journal of Psychiatry*, October 1, 2015

15

Nina R. Schooler, Ph.D.
State University of New York Downstate Medical Center

Scientific Council Member; 1998 NARSAD Distinguished Investigator Grant

Kim T. Mueser, Ph.D.
Boston University

2003 NARSAD Distinguished Investigator Grant

1989, 1988 NARSAD Young Investigator Grant

*Including Mary F. Brunette, M.D., 2000 Young Investigator; Christoph U. Correll, M.D., 2007 Young Investigator; Jennifer D. Gottlieb, Ph.D., 2009 Young Investigator; Robert K. Heinssen, Ph.D., 1990 Young Investigator; Delbert G. Robinson, M.D., 2005 Independent Investigator

Next-Generation Treatment: Psychosis, Schizophrenia

Hopeful News on Comprehensive Team Treatment of Early Psychosis**

Drs. Schooler, Mueser, and five other recipients* of NARSAD grant awards were members of a team that demonstrated that early intervention and coordinated team care can make a real, positive difference in outcomes for first-episode psychosis patients. Over two years, the team treated 223 patients with a protocol called NAVIGATE, a first-episode intervention stressing low-dose antipsychotic medications; cognitive behavioral therapy to support resiliency and illness self-management skills; family psychoeducation and support; and supported employment and educational opportunities. The better outcomes suggest the importance of early and coordinated intervention after a first psychotic episode.

Journal: *American Journal of Psychiatry*, October 20, 2015

The Brain & Behavior Research Foundation is committed to alleviating the suffering of mental illness by awarding grants that will lead to advances and breakthroughs in scientific research. The Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to treat brain and behavior disorders.

Since 1987, the Foundation has awarded more than $342 million to fund more than 4,000 leading scientists around the world. This has led to over $3 billion in additional funding for these scientists. 100% of donor contributions for research are invested in our grants leading to advances and breakthroughs in brain and behavior research. This is made possible by the generous support of two family foundations which cover all of the Foundation's operating expenses.

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