10 Major Discoveries in 2014 by NARSAD Grantees

Potential Diagnostic Biomarker: Depression
New Brain Biomarker Found for Depression Risk in Young Children
Dr. Barch and colleagues including former grantees Joan Luby, M.D. and Kelly Botteron, M.D. discovered the first-ever structural brain biomarker to predict a small child’s risk of having recurrent major depression. They used MRI scans to measure a brain area called the anterior insula (AI). In children at high risk for recurrent major depression (MDD), the volume of the AI was smaller than normal. The effect was especially notable in children who, before reaching school age, had experienced abnormally strong feelings of guilt.
Journal: *JAMA Psychiatry*, November 12, 2014

Basic Research: Autism, Autism Spectrum Disorder (ASD)
Most Comprehensive Study of Rare Autism Mutations To Date
Two studies of DNA sampled from families with one child with autism spectrum disorder (ASD)—the largest of such studies to date—provide the most vivid picture so far of autism’s genetic complexity. Together, they identify dozens of genes not previously linked with autism. The teams predict that at least 300 rare, non-inherited, or “de novo,” gene mutations will be found to play a role in causing autism spectrum disorders. Many of these gene mutations affect synapse formation and gene expression in the developing brain.

Next Generation Therapies: Bipolar Disorder
Fast-Acting Antidepressant Restores Ability to Experience Pleasure in People with Bipolar Disorder
Dr. Zarate and colleagues gave a single dose of ketamine to 36 treatment-resistant patients with bipolar disorder. The drug, experimental in this application, worked remarkably well, reducing anhedonia—feelings of apathy and inability to enjoy oneself—within 40 minutes. The effect lasted up to two weeks and did not correlate with the status of other depressive symptoms. There is no approved treatment for anhedonia, which is also common in schizophrenia, Parkinson’s disease, drug addiction and mood and anxiety disorders.
Journal: *Translational Psychiatry*, October 14, 2014

Next Generation Diagnosis/Treatment: Post-Traumatic Stress Disorder (PTSD)
Brain Imaging Helps Link Specific Symptoms of PTSD with Specific Brain Activity
Using high-resolution PET imaging, Dr. Neumeister and colleagues linked specific symptoms of PTSD, including listlessness and emotional detachment, to low levels of a type of opioid receptor in the amygdala, a brain area where PTSD symptoms are thought to originate. These appear to correlate with lower cortisol levels, suggesting a new role for that stress hormone as a biomarker for certain PTSD symptoms and a possible target for future personalized treatments.
Journal: *JAMA Psychiatry*, September 17, 2014

Basic Research: Autism, Autism Spectrum Disorder (ASD)
Research Showing an Excess of Synapses in Autism
Dr. Peterson and Dr. Sulzer, with colleagues, found a significant overabundance of synapses, or cell-to-cell connections, in the brains of deceased young people diagnosed with autism. This supports the theory that a key event, the pruning of synapses in early brain development, contributes to autism pathology. In mouse models, they traced the possible cause to disruption of a protein called mTOR, and were able to reverse the pathology in the mice with an experimental drug, even after onset of autism-like symptoms.

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10 Major Discoveries (continued)

Next Generation Diagnostics: Suicide Prevention
Foundation-Supported Study Identifies Potential Method for Predicting Suicide Risk with a Blood Test
After identifying an abnormality in a chemical, or “epigenetic,” tag on a gene called SKA2 that correlated with low levels of SKA2 protein in people who had died by suicide, Dr. Kaminsky and colleagues tested blood samples of hundreds of people with histories of suicidal thoughts or attempts. This led to the creation of a model based on the blood test that predicted which of the participants were experiencing suicidal thoughts or had attempted suicide with 80-96 percent accuracy. It will now be tested in larger groups.


Basic Research: Schizophrenia
Largest-Ever Study of Common Gene Disruptions in Schizophrenia
More than 80 institutions participating in the Psychiatric Genomics Consortium (PGC) performed one of the largest biomedical experiments ever, and the largest in mental illness, comparing the DNA of 37,000 people with schizophrenia and 113,000 healthy volunteers. They identified 128 independent genetic associations spanning 108 different “loci,” or areas of the genome where relatively common variations in sequence were associated with schizophrenia. 83 of these loci had not been previously identified. Greater association was found with genes that are expressed in the brain and also among genes with important roles in the functioning of the immune system.


Basic Research/New Technology: Schizophrenia, Autism
Stem Cell Technology Offers Rare Inside View of Brain Development and Schizophrenia
Dr. Ming and Dr. Song, with colleagues, demonstrated the extraordinary power of new iPS (induced pluripotent stem cell) technology to dissect what goes awry in mental illnesses. They “reprogrammed” skin cells sampled from people with a known genetic irregularity previously linked with schizophrenia and autism. These cells were coaxed to develop as brain cells, which enabled the team to find a specific genetic culprit, one missing copy of the CYF1P gene. In mice, the same loss altered the structure of developing brain cells, which in turn disrupted the orderly layers those cells would normally form in the brain.

Journal: Cell Stem Cell, July 3, 2014

Next Generation Therapies: Post-Traumatic Stress Disorder (PTSD)
Discovery Points Toward New Medications to Treat and Potentially Prevent PTSD
Dr. Ressler and team demonstrated in traumatized mice that a medication called osanetant, known to be safe for use in humans, shows potential to treat symptoms of PTSD before they become disabling. The drug disrupts the activity of a gene called Tac2 and is thought to help block the consolidation of fear memory in the brain’s amygdala shortly after exposure to a trauma. Another method, which targets so-called DREADD receptors, was used to lower Tac2 activity, and it too impaired formation of fear memories. This suggests other possible pharmaceutical approaches to achieve the same result.

Journal: Neuron, June 26, 2014

New Technologies: Psychosis, Schizophrenia
Scalp EEG Test May Be Able to Predict Future Psychosis
Dr. Mathalon and team discovered a biomarker in a brain event called mismatch negativity that may predict psychosis. Derived from scalp electroencephalography (EEG) recordings, mismatch negativity is a signal automatically elicited from the brain in response to hearing sounds that deviate from preceding sounds. Believed to reflect the ability to form short-term memory, it is known to be deficient in schizophrenia patients. Experiments revealed mismatch negativity deficits precede the onset of psychosis in high-risk individuals; the larger the deficit, the more likely the risk for conversion to a psychotic disorder.

Journal: Biological Psychiatry, March 15, 2014