Anhedonia, or the inability to feel pleasure or enjoyment, is a key symptom in several mental illnesses including major depression and schizophrenia. This sense of pleasure is generated partly by the brain’s neural pathways involved in seeking and experiencing reward. The new research tells us much more. Using optogenetics to control the activity of dopamine neurons in a part of the brain called the medial prefrontal cortex, the team* was able to produce symptoms of anhedonia in rodents. Brain imaging helped reveal that this cortical reward circuitry can in turn suppress activity in other parts of the brain, such as the striatum, that are involved in reward-seeking behavior.

Research by a large international team that included Drs. Sullivan and O’Donovan, who are leaders of the Psychiatric Genomics Consortium, points to one of the likely causes of schizophrenia in some people: overactive pruning of synapses - connections between nerve cells - in the brain’s prefrontal cortex during the early years of life. The team focused on variation in genes giving rise to a vital group of proteins called the major histocompatibility complex (MHC). MHC proteins are part of the mechanism used by the immune system to fight off foreign invaders. The team found that variations in the expression of genes known as complement component 4 (C4) genes specifically impacted neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. Excessive C4 activity may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.
NEW TECHNOLOGY: AUTISM, SCHIZOPHRENIA, INTELLECTUAL DISABILITY

Genetic Anomalies Frequently Associated with Neurodevelopmental Disorders Can Now Be Efficiently Recreated in the Lab

A new method for recreating large-scale genetic anomalies known as copy number variations (CNVs) will make it easier for scientists to study the effects of those mutations, many of which have been linked to autism and other neurodevelopmental disorders. Drs. Gusella, Talkowski and colleagues have already used the approach, called SCORE, to create human cells that carry too many or too few copies of chromosomal regions known as 15q13.3 and 16p11.2 – CNVs associated with disorders such as autism, schizophrenia, and intellectual disability. The achievement paves the way for studying exactly what goes wrong in cells that carry such defects, and could help researchers find ways to correct those problems. SCORE is an important application of CRISPR, a research tool that is changing the way scientists “edit” genomes in the lab.

JOURNAL: Nature Neuroscience February 1, 2016

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NEXT-GENERATION TREATMENTS: DEPRESSION

Opioid Medication Combo Helps Patients Who Don’t Respond to Antidepressants

Reviving an old treatment for mood problems, researchers find that adding certain opioid medications to depression treatment can help patients who don’t respond well to conventional antidepressants. When Dr. Fava’s team gave a combination of opioid medication and antidepressants as an adjunct therapy to patients who had not responded to antidepressants alone, these patients saw greater improvements than their peers who received only antidepressants. The drug combination consisted of buprenorphine, an opioid medication, and samidorphan, an opioid antagonist included to block those effects of buprenorphine that are associated with its addictive potential. All patients continued on their current antidepressant therapy and on the same dosage throughout the course of the study.


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NEXT-GENERATION TREATMENTS: SUICIDE, DEPRESSION

Important Discovery by Foundation-Supported Researchers Explains How Ketamine Exerts its Rapid Antidepressant Effects

Ketamine, a drug approved long ago as an anesthetic but used recently on an experimental basis to treat resistant major depression, exerts rapid antidepressant effects in many patients, including those contemplating suicide. The new research suggests it may be possible to separate ketamine’s benefits from its serious unwanted side effects. Inside the body, ketamine is broken down and forms several new compounds, called metabolites. The team discovered that one of these metabolites—a molecule called hydroxynorketamine (HNK)—can by itself generate the antidepressant effects seen in ketamine. Efforts are under way to develop and test an HNK-like drug in animals and then people.


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**NEXT-GENERATION TREATMENTS: MULTIPLE ILLNESSES**

**Treatment with Immune-Regulating Gut Bacteria May Boost Immune System Against Stress**

Risk for psychiatric disorders ranging from depression to PTSD to schizophrenia is thought by some scientists to be linked to elevated levels of inflammation. By exposing mice to bacteria that help regulate the immune system, a team* led by Dr. Lowry was able to prevent stress from causing harmful inflammation, and in some cases, symptoms of illness. The researchers injected mice with a bacterium called *M. vaccae*, which is abundant in soil and has immune system-regulating effects. This prevented mice from getting colitis when put in highly stressful situations. In stressed mice, the treatment had anti-anxiety and fear-reducing effects. The findings can help researchers develop microbiome- and immunoregulation-based strategies to prevent disorders related to stress.

**JOURNAL:** Proceedings of the National Academy of Sciences, May 31, 2016

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**NEXT-GENERATION TREATMENTS: DEPRESSION**

**Brief Course of Psychotherapy Benefits Moms with Major Depression and Their Children**

Children whose mothers have depression are more likely than others to develop childhood psychiatric illnesses. Dr. Swartz and colleagues now show that these children do better when their mothers are treated for depression and their symptoms improve. Previously, such studies had involved women whose depression was treated with medication, not psychotherapy. 168 mothers participated in nine 45-minute psychotherapy sessions over three months. For one group, the therapy was specifically focused on the mother’s relationship with her child. Treatments helped all mothers, but those children whose mothers were in the latter group had fewer mental health visits and were prescribed fewer antidepressant medications during the study than children whose mothers underwent the general therapy.

**JOURNAL:** Journal of the American Academy of Child & Adolescent Psychiatry, June 2016

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**EARLY INTERVENTION/DIAGNOSTIC TOOLS: PSYCHOSIS**

**New Tool Calculates Patients’ Personal Psychosis Risk**

Most people who develop schizophrenia and other disorders involving psychosis (including some cases of bipolar disorder and depression) experience subtle changes in belief, thought, and perception that precede the onset of full psychosis. But fewer than 35 percent of people with these subtle changes actually develop full psychosis within three years of being identified as high-risk. Those who do become ill fare best when treated early. A team* led by Dr. Cannon developed a new risk calculator to identify them, using data from 596 high-risk individuals. Dr. Carrión led another team* that validated the risk calculator in a separate group of 210 high-risk individuals. The most important warning signs were: higher levels of unusual thought content and suspiciousness, as compared with others; lower verbal learning and memory capacity, slower cognitive processing, and greater decline in social functioning.

**JOURNAL:** American Journal of Psychiatry, July 1, 2016 [both papers]

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Dr. Carrión’s team included 2004 Young Investigator Andrea Auther, Ph.D.; Scientific Council Member, 2001 Klerman Prizewinner, and 2007 Distinguished Investigator, 1997 & 1994 Young Investigator, Cameron S. Carter, M.D.; 2012 Young Investigator Tara A. Niendam, Ph.D.; and 1996 Young Investigator Stephan F. Taylor, M.D.
**NEXT-GENERATION TREATMENTS: DEPRESSION**

Treat Metabolic Problems Improves Symptoms of Some Patients with Refractory Depression

Dr. Pan and colleagues* have discovered that some people who suffer from major depression may benefit from the diagnosis and treatment of metabolic deficiencies. These are abnormal levels of the byproducts of basic bodily and cellular functions -- in this case as detected in the blood, plasma, urine, and cerebrospinal fluid (which circulates in the spinal cord and brain). In a study of patients with treatment-resistant depression, about two-thirds had metabolic deficiencies that affect the brain’s ability to produce neurotransmitters. Patients’ depression symptoms declined significantly when these metabolic problems were treated. Some reached remission. The most common of the deficiencies observed in participants was in levels of cerebral folate, which is treatable with folinic acid.

**JOURNAL:** *American Journal of Psychiatry* August 13, 2016

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**BASIC RESEARCH: SCHIZOPHRENIA**

Researchers Catalog Subtle but Widespread Schizophrenia-Associated Differences in Gene Activity

Dr. Sklar led a large team* that identified nearly 700 genes whose activity levels differ in the brains of people with schizophrenia compared to those without it. Most of the differences were subtle, consistent with the idea that variations in many genes contribute to the risk of schizophrenia, each alone having a small effect. The team compared the activity of genes within the brain whose sequences had previously been shown to vary in small but significant numbers of patients. They manipulated the activity of five of the schizophrenia-linked genes in zebrafish (a “model organism” often used for genetics experiments), and found three genes whose alteration disrupted brain development. Other researchers can now extend the team’s findings by further exploring genes on the list to begin teasing out the molecular basis of schizophrenia.

**JOURNAL:** *Nature Neuroscience* September 26, 2016

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