going deep with
PARKINSON’S DISEASE

PLUS
UNDERSTANDING THE BIOLOGY BEHIND DEPRESSION
A NEW TREATMENT FOR PTSD
TRAUMA AND WOMEN’S BRAINS
COHEN BRAIN COLLECTION
HIGH-IMPACT RESEARCH
Conducting state-of-the-art scientific investigation to maximize discovery and accelerate translation of findings towards achieving prevention and cures is a core element of the McLean Hospital mission. Demonstrating that commitment, we have developed the new publication you are reading today. This inaugural edition and those to follow will focus exclusively on the cutting-edge research taking place here at McLean.

Thank you to all the donors who help fund this research. Without you, we would not be able to make the important advances described herein.

Included in our first edition are stories about personalized stem cell therapy for Parkinson’s disease, the biology behind major depressive disorder, a potential new treatment for PTSD, and how trauma affects women’s brains. I hope that you find this publication to be valuable and interesting.

If you would like to provide feedback about this new publication or if I can be of service to you in any other way, please do not hesitate to contact me directly at kressler@mclean.harvard.edu.

FROM THE BENCHTOP OF CHIEF SCIENTIFIC OFFICER KERRY J. RESSLER, MD, PhD

McLEAN RESEARCH BY THE NUMBERS

1,704
Number of research papers authored by McLean investigators that appeared in peer-reviewed journals in the last five years

344
The number of full-time employees involved in research and affiliated programs at McLean Hospital

108,103
Amount of square footage dedicated to psychiatric and neurodegenerative research

50
Number of research labs at McLean Hospital

Research Activity Mix

54%
Basic Research Science

26%
Other Clinical Research

12%
Clinical Trials

8%
Training/Other
PERSONALIZING STEM CELL THERAPY FOR PARKINSON’S DISEASE

In the United States alone, as many as one million people have Parkinson’s disease (PD), with approximately 60,000 cases being diagnosed each year, according to the Parkinson’s Disease Foundation. Kwang-Soo Kim, PhD, director of the Molecular Neurobiology Laboratory at McLean Hospital and professor of psychiatry at Harvard Medical School, pictured above, is committed to finding a way to lower those numbers.

Kim’s team is at the forefront of investigating personalized, stem cell-based therapy for PD. He has developed a novel, highly efficient, and safe way to reprogram patients’ own cells to become functioning midbrain dopamine cells—the cells whose loss primarily causes the disease. These cells, which produce the neurotransmitter dopamine, occupy a specific area in the brain’s substantia nigra and project into the dorsal striatum, forming the so-called nigrostriatal pathway. This is the major neuronal pathway controlling human movement, with its disruption leading to the tremors, stiffness, gait changes, and difficulty initiating movements that characterize PD.
Kim’s method overcomes the limitations of other stem cell therapies for PD. It uses patients’ own cells, derived from their skin and transformed into induced pluripotent stem (iPS) cells—cells that behave like embryonic stem cells in that they can develop into practically any cell type. The strategy eliminates not just the possibility of immune rejection but also the ethical issues tied to embryonic stem cell research. It relies on non-viral, footprint-free methods to reprogram the skin cells (such as protein-based or plasmid-based methods) rather than the standard viral delivery system that carries the risk of disrupting patients’ chromosomal DNA and canceling out tumor suppressor genes or activating cancer-causing ones.

Finally, his method removes any remaining “undifferentiated” cells—those that have not yet become a specific cell type—before transplantation, thereby prohibiting tumor formation. Kim’s group added this important step when they discovered that several small molecules, including the natural compound quercetin, selectively kill undifferentiated stem cells. They do so by targeting the survivin gene (BIRC5), which is specifically abundant in undifferentiated cells.

“...the most important criterion is safety,” said Kim. “We now have a very robust, optimized protocol for iPS cell-based autologous cell therapy. Many studies have shown that tumor formation after transplantation is directly proportional to the amount of remaining undifferentiated cells. Our method removes them completely. And by using a non-viral method to reprogram the iPS cells, we can maintain the cells’ genetic integrity.”

The Role of Dopamine in Parkinson’s Disease

Kim has been studying the molecular biology of dopamine neuronal systems for more than 25 years, 18 of them at McLean. His research at the hospital concentrates on the development and maintenance of the neurons themselves. “What makes a dopamine neuron become a dopamine neuron?” he said, describing it as the burning question he wanted to address. “What goes wrong with dopamine neurons in the case of disease?”

Turning to stem cell research to answer these questions was a natural progression. Stem cells are essentially a tabula rasa: they can give rise, through the process of differentiation, to any kind of specialized cell, for example, a heart, liver, or muscle cell, depending on how the stem cell’s genes interact with the physical and chemical conditions in its environment.

Kim set out to find what would turn stem cells into the specific dopamine cells degenerating in PD—midbrain dopamine (mDA) neurons in the substantia nigra. He initially used mouse embryonic stem cells to generate mDA neurons and transplanted them into the brains of mice or rats engineered to have traits of PD.

“We could see that this transplantation had the potential to rescue the motor function defect in the animals,” said Kim. “But at the same time, there were some very significant limitations in that some of the animals developed tumors, and differentiation to mDA cells was not very efficient.”

In 2009, he shifted his attention to human iPS cells generated from human skin cells. Using a direct protein method to deliver the genes that would trigger the transformation eliminated the risk of disrupting the cells’ chromosomal DNA, but the process was slow, and the produced iPS cells varied in their ability to differentiate into mDA neurons.

Recently, Kim and his colleagues discovered a fundamental mechanism underlying the change in metabolic properties that accompanies the skin cells’ reprogramming. The finding enabled them to develop a novel reprogramming method, for which they are awaiting a patent.

“My hope is that in the not too distant future we will be ready to run a human clinical trial.”
– Kwang-Soo Kim, PhD

Optimizing the Differentiation Protocol

Differentiating iPS cells into particular cell types is tricky, but Kim’s lab has gone a long way toward doing so, spending countless hours bent over petri dishes investigating which
signals transform them into functional mDA neurons. One of these differentiation technologies was recently licensed to the stem cell company Cellular Dynamics, based in Madison, Wisconsin, and the protocol itself is patent pending.

“My lab is continuing to optimize the differentiation protocol, because if you think about brain development, there are maybe tens or even hundreds of different signals taking place in a temporal-specific manner, in a gradient-specific manner, in a combinatorial manner to drive specific neuronal lineages,” said Kim. “We now have an effective protocol that can make large proportions of mDA neurons.”

The current challenge is to test the human mDA neurons in an animal model to determine the best stage at which to transplant them and how many to transplant to reverse Parkinson’s effects. For that, Kim and his colleagues are using the popular 6-OHDA lesion rat model. The researchers inject the chemical 6-OHDA, which kills dopamine neurons, into one side of the nigrostriatal pathway, causing a lesion and stopping dopamine function. Behaviorally, upon administration of apomorphine, the rat will rotate to the lesion side, as movements will now be driven by the intact side. They then inject the new mDA neurons into the lesion side, wait three to four months for the transplant to “take” and new neurons to grow, and make careful computer-generated measurements of the rat’s rotation recovery. Later they sacrifice the animals to analyze the extent of the neuronal growth in their brains and how that growth relates to the elimination of symptoms.

“With all this analysis, we can come up with the most accurate calculations for real transplant conditions,” said Kim. “My hope is that in the not too distant future we will be ready to run a human clinical trial.”

**RESEARCH NEWS BRIEFS**

**McLEAN WELCOMES NEW MRI SCANNER**
Recent improvements in MRI technology hold tremendous potential for the study of brain function, particularly how it relates to addiction and mental illness.

McLean’s new Siemens Prisma 3T MRI scanner combines a powerful 3 Tesla magnet with a variety of features to create a machine that offers a full range of clinical and research applications.

Scott E. Lukas, PhD, director of the McLean Imaging Center (MIC), explained that the Prisma has “advanced electronics, sophisticated switching, and superior gradients so we can make images more precise than ever before.” In addition, the machine contains features that create a quieter, more relaxing experience for patients, which saves time and produces better results.

“It’s faster, better, more precise,” said Diego A. Pizzagalli, PhD, director of the MIC. “It gives us more capability to study brain function, chemistry, and structure.”

**ADVANCING PTSD AND TBI RESEARCH**
McLean Hospital, in partnership with Cohen Veterans Bioscience, has established a vital collection of postmortem brains to be used in research on post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) in veteran and civilian populations.

According to McLean’s Chief Scientific Officer Kerry J. Ressler, MD, PhD, who along with colleague Sabina Berretta, MD, scientific director for the Harvard Brain Tissue Resource Center (HBTRC) at McLean, will be overseeing the new PTSD and TBI collection, there is an overwhelming need for postmortem research on these two afflictions.

“Through understanding these molecular and cellular differences, we will be able to develop new therapeutic approaches for intervention, prevention, and treatment of people with PTSD and TBI,” said Ressler.

The collection—known as the Cohen Brain Collection—will be maintained at HBTRC, which oversees the distribution of postmortem brain tissue to the scientific community for the purpose of conducting brain research.

**PARTNERS HEALTHCARE BIOBANK**
McLean and hospitals affiliated with Partners HealthCare, including Massachusetts General Hospital and Brigham and Women’s Hospital, have joined forces to create the Partners HealthCare Biobank. This large research data and sample repository—available to approved investigators at Partners institutions—provides researchers with access to high-quality, consented samples to bolster research, advance our understanding of the causes of common diseases, and advance the practice of medicine. Data quality is only as good as the raw materials, and by using consented, annotated, and high-quality samples, investigators can generate high-quality data.

For this new database, patients simply volunteer their blood samples and complete a health information survey to help researchers understand how mental and physical health is affected by genes. To date, 2,000 McLean patients have agreed to participate in the program.
Major depressive disorder (MDD) affects about seven percent of people in the United States each year. Although researchers and clinicians know that stressful life events can trigger a depressive episode, the biological mechanisms behind it are not well understood. Studies led by Diego A. Pizzagalli, PhD, director of the Center for Depression, Anxiety and Stress Research (CDASR) at McLean Hospital, aim to reveal how depression changes the brain, enabling clinicians to identify people who are prone to the disorder and predict the possibility of recurrent episodes. "If we are able to predict the first onset of depression, we will hopefully one day be able to prevent it," said Pizzagalli.

MDD is caused by a complex interaction of personality traits, genetic predisposition, and life history, including adverse childhood experiences such as neglect or abuse and stressful events often coupled with feelings of entrapment. "Depression is multifactorial," said Pizzagalli. "That's the model that we embrace within the CDASR. We don't just study biology or psychology. We also study the environment, genetics, the brain, behavior, and stress. We assess all of these variables because we believe they are all important in understanding depression."

Pizzagalli, who also directs the McLean Imaging Center, uses a variety of imaging techniques to map and describe the brains of people with MDD as well as people who might develop the disorder down the line. To understand why MDD occurs, he believes it is also important to understand why it re-occurs—a distinctive feature of the disorder. When people experience their first major depressive episode, it is usually after a traumatic or stressful life event. But the more relapses
a person has, the more likely he or she is to experience an episode without a traditional trigger.

“With every episode, psychologically or biologically, something changes that then leaves people vulnerable to future episodes,” said Pizzagalli. “People become sensitized.” The process, he said, could be described as a scar susceptible to re-injury. “We want to know: can we predict an initial episode? can we predict a relapse? why do later episodes become more uncoupled from stress?”

To answer some of those questions, Pizzagalli teamed up with Roee Admon, PhD, a research fellow at the CDASR.

In one study, Pizzagalli and Admon tested the ways past depression influenced future happiness. They had two groups of people—some who had experienced depression, and some who had not—complete a humor comprehension task, which had been modified to provide an abundant amount of positive feedback. They found that when they were told they had answered the question correctly, people who had been depressed were just as happy as those who never had been. But crucially, the people who had experienced depression stayed happy for a shorter period of time relative to those without a prior history of depression.

While the study was conducted, the participants’ brain activity was monitored using functional magnetic resonance imaging (fMRI). The same subjects who were happy for a shorter time also showed less activation in the nucleus accumbens, a part of the brain associated with the pleasure response, happiness, and motivation. Ultimately, Pizzagalli wants to see if activity in the nucleus accumbens may predict the likelihood of a relapse.

Another part of the brain associated with reward that his lab focuses on is the putamen. In particular, he investigates the putamen’s role in personality traits related to depression such as anhedonia, the loss of interest in previously enjoyable activities. “Some people, for some reason, are more anhedonic than others, meaning they tend to be less responsive to the good things that happen in their lives,” said Pizzagalli. “Research shows that anhedonia can be a precursor to depression and also predict poorer outcomes in treatment.”

Currently, Pizzagalli is working on a long-term study that plans to track 186 adolescents—half with family histories of MDD and half without—over time to see who develops depression, using imaging technology to monitor chemical and biological changes in the brain. In addition to using fMRI, Pizzagalli and his colleagues are using proton magnetic resonance spectroscopy, which allows them to study neurochemicals in the brain. So far, they have found that reduced putamen size predicts anhedonia three months into the future.

None of this is definitive, Pizzagalli noted. There is still a lot of research to be done. He and his colleagues plan to follow the adolescents to identify how stress relates to structural and neurochemical changes in the brain, including disruptions in dopamine signaling, a neurotransmitter involved in reward pathways, and how these changes might predict anhedonic symptoms. In 2016, Pizzagalli received a Method to Extend Research in Time (MERIT) award from the National Institute of Mental Health to continue this long-range research.

It is Pizzagalli’s hope that his work will not just help predict who might have depression but will also advance development of personalized treatments. It is known that some antidepressants work for certain people, while different ones might work better for others. It is possible that this might result from underlying neurological differences. For example, in some of his past research, Pizzagalli found a relationship between the number of depressive episodes a person had and the volume of the hippocampus and medial prefrontal cortex, both of which are involved in how a person responds to stress. It is unclear if the reduced size causes the depression, or vice-versa, but it is possible that antidepressants, which increase the size of these brain regions, might help. Past research—not conducted by Pizzagalli—has found that successful treatment with antidepressants is associated with an increase in hippocampal volume. Pizzagalli thinks that one day it might be possible to look at the neurological changes underlying a person’s depression and prescribe a personalized treatment.

“We want to know: can we predict an initial episode? can we predict a relapse? why do later episodes become more uncoupled from stress?”

– Diego A. Pizzagalli, PhD

Currently, there’s no way to unambiguously predict whether people will respond to treatment,” he said. But with neurological maps of the mechanisms driving depression, like the ones Pizzagalli is developing, that could change.

“In other fields of medicine, such as cancer treatments, you use an array of variables and information to guide treatment selection,” said Pizzagalli. “If we can develop a psychological and biological profile of people with MDD, we could recommend specific treatment regimens for them.”
With new discoveries by McLean Hospital researchers, a fast and effective treatment for PTSD, anxiety, and addiction disorders could be close at hand. Literally.

Right now, work is underway to develop a handheld inhaler containing xenon gas that could be used to block traumatic memories as soon as they are experienced. Whether used in a clinical setting or self-administered in the real world, the treatment could “help PTSD patients and others be better able to cope with the emotional toll of re-experiencing their trauma memories,” according to Edward G. Meloni, PhD, an investigator in the Behavioral Genetics Laboratory at McLean Hospital and an assistant professor of psychiatry at Harvard Medical School.

Meloni and his colleague Marc J. Kaufman, PhD, director of the Translational Imaging Laboratory at McLean Hospital and an associate professor of psychiatry at Harvard Medical School, were recently issued a patent allowance for their invention covering the use of xenon to treat psychiatric illnesses such as PTSD. Now the researchers are working with the biotech firm Nobilis Therapeutics on the development and testing of a portable administration device as well as devising other uses for the invention to help individuals with a range of neurological and psychiatric disorders. Also, Meloni and Kaufman are preparing to move beyond the initial animal testing that led to their invention and study the effects of xenon gas on human patients.

The invention, Kaufman explained, grew out of research “to see if xenon could protect against some of the natural processes in the brain that cause Parkinson’s disease.” A series of setbacks slowed their investigations into Parkinson’s, but triggered a new line of inquiry—the potential impact of xenon gas on PTSD and anxiety disorders.

The researchers hypothesized that xenon, which can affect multiple brain systems involved in memory formation, had potential for targeting parts of the brain that store and process aversive memories. To test their hypothesis, Kaufman and Meloni began to investigate the impact of xenon through a series of experiments on rats. In a controlled environment, rats

“We want to prove that it is effective and can be part of regular therapy for people who are really suffering with this disorder.”

– Edward G. Meloni, PhD
were exposed to an aversive event—a brief footshock—after hearing a loud tone. In this way, the rats were conditioned to fear the tone much in the same way a person may acquire fear to stimuli associated with a traumatic experience. Then, the researchers conducted experiments in which xenon gas was introduced into the rats’ environment after hearing the tone. They found that xenon greatly reduced the fearful responses in the subjects who were re-exposed to the tone.

Based on their findings, the researchers came to believe that xenon had potential for treating people with PTSD and related conditions. Just as xenon helped the rats forget the traumatic memory triggered by the tone, Meloni said “xenon gas could modulate the memories of an individual after experiencing a troubling flashback or nightmare.”

“Applying xenon gas right after someone experiences a traumatic memory could help inhibit a natural process called ‘reconsolidation’ or the process in which memories are re-remembered or restored,” he explained.

Because xenon gas may be able to modulate fear-related memories, the researchers believe their invention could augment commonly used treatments for PTSD, which focus on medication and cognitive behavioral therapy in a clinician’s office. Unfortunately, the use of standard antidepressants alone “does not get at the core pathology of what’s sustaining PTSD” and are only effective in roughly half of people with the condition. For the other half, Meloni stated, “the brain just recalls the trauma, reconsolidates it, and doesn’t extinguish it.” By using xenon gas as a supplement to the standard of care, an individual could “inhale xenon at the end of a therapy session, and it would help prevent the reconsolidation process, maybe even facilitate the extinction process,” he said.

For flashbacks and nightmares that occur outside of the therapist’s office, the gas could be self-administered with an inhaler. “Using xenon with a handheld device by the bedside could be the perfect thing to help someone who wakes up with a disturbing memory,” Kaufman explained. The gas, he said, “works and dissipates quickly.”

Clinical trials on individuals with PTSD are now being organized. In upcoming studies to be funded by Nobilis, police officers, firefighters, active members of the military, first responders, and others who come to McLean Hospital for PTSD treatment in the LEADER program can enroll in a study that will use xenon in conjunction with trauma memory reactivation sessions.

“We’ll have them talk about their trauma, and we’ll tape the sessions,” Meloni said. The tapes will then be played back to the patient to reactivate the memory. Emotional and physical responses will be recorded, and xenon will then be introduced using a handheld device “to see if we can interfere with the brain’s ability to reconsolidate these painful memories and potentially begin a natural mental healing process,” he explained. The individuals will be brought back a week later and asked if they are still experiencing nightmares, thoughts of suicide, or continuing traumatic memories. In all, study participants will take part in six rounds of therapy and xenon exposure and followed for up to six months to document recovery.

“This study is our proof of concept, our way of seeing if xenon makes people with PTSD feel better,” Meloni said. “Already, existing data shows that the treatment is very safe. Now we want to prove that it is effective and can be part of regular therapy for people who are suffering with this disorder.”

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HIGH VOLUME AND HIGH IMPACT:
McLEAN RESEARCHERS WITH MORE THAN 10,000 RESEARCH PAPER CITATIONS

Conducting state-of-the-art scientific investigation to maximize discovery and accelerate translation of findings towards achieving prevention and cures is a critical component of McLean’s mission. Exemplifying this drive, below is a list of just a few of our many staff who have compiled more than 10,000 paper citations.

Francine M. Benes, MD, PhD  Harrison G. Pope, MD, MPH
Bruce M. Cohen, MD, PhD  Scott L. Rauch, MD
Joseph T. Coyle, MD  Kerry J. Ressler, MD, PhD
John G. Gunderson, MD  Martin Teicher, MD, PhD
James I. Hudson, MD, ScD, SM  Mary C. Zanarini, EdD
Through clinical practice and neuroimaging studies, McLean Hospital’s Milissa Kaufman, MD, PhD, and Lauren A.M. Lebois, PhD, are revealing the clinical, cognitive, and neurobiological underpinnings of the effect of trauma on the brain, specifically in women, including long-misunderstood forms of post-traumatic stress disorder (PTSD)—PTSD dissociative subtype and dissociative identity disorder (DID). In so doing, they are not only helping to destigmatize the disorders, which often develop as a defense against early abuse and neglect, but are also identifying risk factors for them. They are also opening the door to more targeted treatments in the future.

“These women are often marginalized because of their diagnosis,” said Kaufman, who is director of McLean’s Dissociative Disorders and Trauma Research Program and medical director of the hospital’s Hill Center for Women. “By understanding the neurobiology of dissociation we can help destigmatize people with dissociative disorders and PTSD and also destigmatize child abuse and women who have been abused.”

To those ends, she and Lebois, director of neuroimaging in the Dissociative Disorders and Trauma Research Program and a fellow in the Neurobiology of Fear Laboratory, have embarked on an ambitious research study funded by a two-year Exploratory/Developmental Research Grant Award from the National Institutes of Health. In the study, they will expand on preliminary research exploring the relationship between the phenomenology (the subjective experience) of women with these disorders and the neural mechanisms that represent three forms of PTSD: classic PTSD, the dissociative subtype, and DID.

“There is no better way to understand just what trauma means to a person than to listen deeply to his or her own words,” said Kaufman.

For the neuroimaging component, participants, both those with diagnoses and those who serve as controls, will take part in various paradigms while undergoing functional magnetic resonance imaging. The paradigms include: a challenging attention task to learn if dissociation is associated with increased attentional control; an emotional probe in which participants view fearful, angry, and happy faces to reveal differences in how the brain processes information relative to specific diagnoses; and a resting state scan.

“In the resting state scan, subjects lie still and think about nothing in particular, which means they daydream,” said Lebois. “That enables us to see how the different networks in the brain talk to each other. We want to know: is there

HOW DOES TRAUMA AFFECT WOMEN’S BRAINS?
a difference in connectivity in people that have PTSD, the dissociative subtype, and DID?”

The researchers will also look at how genetic variability might influence the expression of dissociative symptoms in adult survivors of childhood trauma. “We will be taking saliva samples to investigate candidate genes—genes that have been shown in a small number of studies to possibly be associated with dissociation,” said Kaufman.

Expanding Paradigms, Diagnostic Limitations

Past research—both clinical and carefully conducted neuroimaging provocation studies—provides insight into the symptoms and neurobiological correlates of PTSD. With their large-scale, cross-sectional study, Kaufman and Lebois are significantly expanding the paradigms and forms of dissociation that have been investigated to take those insights to the next level.

“**There is no better way to understand just what trauma means to a person than to listen deeply to his or her own words.”**

– Milissa Kaufman, MD, PhD

Classic PTSD is characterized by intrusive flashbacks, avoidance of salient reminders, and a constant state of high arousal and reactivity. It often results from an adult onset trauma, such as that experienced by a young woman Kaufman described who had witnessed a suspected gang-related shooting. “Following the event, she became hypervigilant, on guard all the time, ready to act,” said Kaufman. “Triggers of threats seemed to be everywhere.”

Among many brain regions, three key areas of the brain often take center stage in PTSD, explained Lebois: the ventromedial prefrontal cortex, which relates to executive function, cognitive control, and extinction learning, among other roles; the amygdala, which acts as what Lebois calls “a salience detector,” detecting important events and objects in the environment; and the insula, which is involved with self-referential processing, such as monitoring internal bodily states.

Lebois explained that when someone without PTSD experiences a threat, the amygdala fires up and signals other parts of the brain, including the brain stem and the motor cortex, to join forces to “coordinate a full-bodied stress response to deal with the threat.” When the threat passes, the ventromedial prefrontal cortex comes back on line, inhibiting amygdala activity. “In essence, the ventromedial prefrontal cortex is putting the brakes on amygdala activity,” she said.

With classic PTSD, however, communication between the amygdala and the ventromedial prefrontal cortex breaks down, permitting the amygdala to continue “running wild,” as Lebois puts it, even though the threat has passed.

A person diagnosed with the PTSD dissociative subtype exhibits the same symptoms as someone with classic PTSD plus two more—depersonalization and derealization. Kaufman described a young woman who exhibited this subtype following a brutal physical and sexual assault. “Her whole worldview had changed,” said Kaufman.

She had a striking sense of detachment from her thoughts, emotions, surroundings, and even her own body. “She knew she’d been assaulted, could remember details of the attack, but experienced it from a distance, as if she were watching herself undergo the trauma, feeling nothing,” Kaufman said.

The neurobiology here is the opposite of that in the classic case, said Lebois. “Instead of the amygdala being hyperactive and the ventromedial prefrontal cortex being hypoactive, the situation is reversed: the brakes that the ventromedial prefrontal cortex put on the amygdala stay on, keeping the amygdala from mounting a bodily stress response.”

People with DID exhibit all of the above symptoms plus a disruption of identity and recurrent gaps in recall. Such dissociation, Kaufman and Lebois stress, is nothing like the media portrayals of those with so-called multiple personalities. Rather, the person behaves in a way that, to their confusion, seems to be “not me,” said Kaufman, “as if someone inside her jumped out and acted in uncharacteristic ways. There is marked discontinuity in one’s own sense of self and one’s own sense of agency.”

People with DID may make hard transitions between distinct behavioral states—for example, numb vs. intensely triggered. “The way of thinking is more compartmentalized,” said Kaufman.

The compartmentalization that characterizes dissociation can be a great defense mechanism—it can keep people feeling removed from their trauma and able to function in the world. However, when it goes too far or when triggers hit, said Kaufman, “it can wreak havoc on people’s lives.”

In the study, Kaufman and Lebois are collaborating with colleagues from across disciplines at McLean to broaden the reach of research into dissociative disorders.

“We have found that one of the most gratifying aspects of doing this research is how willing and open and grateful the women are to participate,” said Kaufman. “They feel like they’re giving back. It’s not easy because we’re asking them about their trauma history. It can be painful. But to a person, they have felt they are being helpful to others. These are people who don’t get asked about their stories. They’re glad someone is doing so now.”

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McLean Hospital is honored to be ranked #1 in psychiatry by U.S. News & World Report.