


DISCOVERY

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11.2019



THE PTSD ISSUE

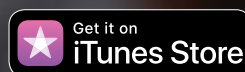


ON THE AIR: MINDFUL THINGS

Tune in to Mindful Things, McLean Hospital's thought-provoking and informative podcast that explores mental health through frank, in-depth, personal, and sometimes difficult conversations.

The series features a wide variety of guests, including clinicians, advocates, and celebrities, and covers a wide breadth of topics, such as depression, anxiety, and trauma, with virtually no subject being off-limits.

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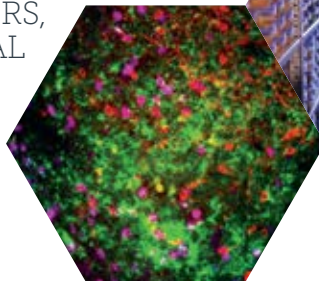
An update on the breakthroughs that McLean's researchers are making in identifying the roots of PTSD.

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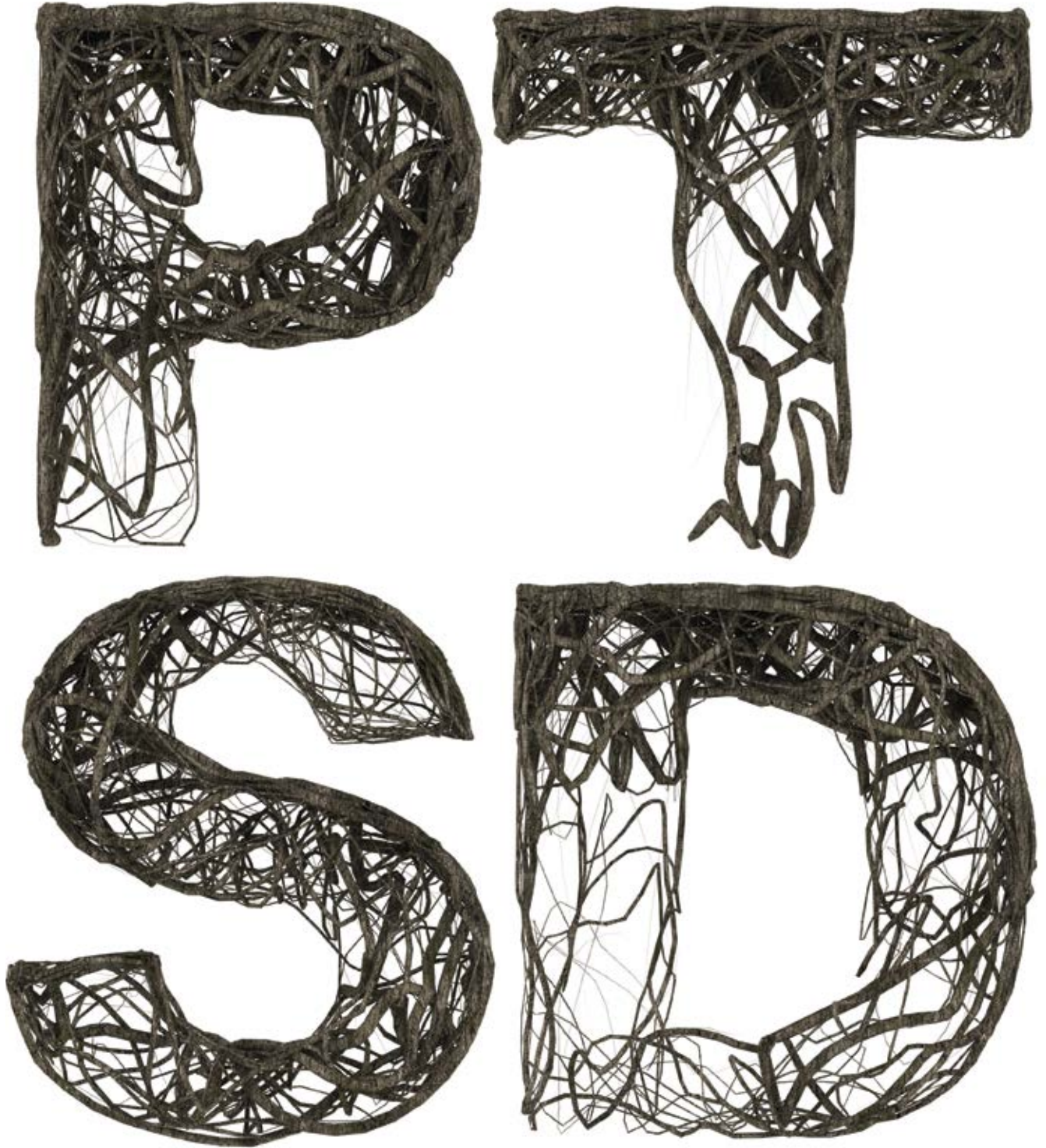
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IDENTIFYING THE ROOTS OF PTSD



SURVIVAL. In an animal kingdom enriched by a diversity of species, it is the one trait shared by organisms as simple as worms and as complex as humans. And the proof is in a protein with the hopelessly complex name of pituitary adenylate cyclase-activating polypeptide.

Commonly referred to by scientists as PACAP, this neuropeptide—and its interactions with the corticotropin-releasing factor (CRF) that regulates the stress hormone cortisol—are at the center of a 5-year, \$13.5 million research effort at McLean Hospital, where the Silvio O. Conte Center for Basic Neuroscience was recently established. The Conte Center, funded via a massive new grant from the National Institute of Mental Health, will aim to better understand the biological roots of post-traumatic stress disorder (PTSD) and other trauma- and stress-related disorders, including depression.

What makes this project unique is that it will look at stress and PTSD through the interaction of these compounds—at the molecular and brain circuit level—via animal studies focusing on fear responses; by examining the relationship to sleep and circadian rhythms; and via a human clinical study involving patients with PTSD. It will also bring in young researchers, from local colleges with strong neuroscience programs, to educate the public.

According to the Substance Abuse and Mental Health Services Administration, in the United States, 61% of men and 51% of women report exposure to at least one traumatic event in their lifetime. Violence and abuse—whether via war, traffic accidents, physical attacks, child abuse, or sexual abuse—are the primary triggers of significant stress. For 5 to 10% of the population, key symptoms can persist after a month, a sign of PTSD.

Nightmares and flashbacks are widely recognized symptoms of

a person re-experiencing trauma. It also presents itself as other problems, such as being constantly on edge or having trouble sleeping. Finally, a person with PTSD exhibits thought or mood problems, having trouble focusing and experiencing feelings of low self-esteem.

A foundation of the project is recognition that all animals exhibit what is commonly known as the fight-or-flight response, expressed in specific regions of the brain and triggered by chemical responses involving neuropeptides, small protein-like molecules used by neurons to communicate with each other. Different neuropeptides are involved in a wide range of brain functions, including pain,



THIS WORK HAS
THE POTENTIAL TO
REVOLUTIONIZE
THE WAY IN WHICH
CLINICIANS DELIVER
CARE TO THEIR
PATIENTS



reward, food intake, metabolism, reproduction, social behaviors, learning, and memory.

PACAP is “involved in the important function of species survival,” said Edward G. Meloni, PhD, one of the principal investigators of the Conte Center. Meloni started PACAP research at McLean over a decade ago, providing a foundation for what is now one of the world’s premier research centers focusing on this peptide.

“If you administer CRF or PACAP to animals, they show the hallmark signs of stress, including fear, anxiety, and aggression,” explained Bill Carlezon, PhD, chief of the Basic Neuroscience Division and director of the Behavioral Genetics Laboratory at McLean. “Our basic hypothesis is that these peptides

work together and can substitute for one another. It’s not an especially complicated idea, but very few research teams prioritize studying peptides in tandem in this way.”

But while most animals recover the next day after receiving CRF, it can take 3-4 weeks to recover after administration of PACAP, he explained. “The consequences of PACAP are persistent and enduring—just like conditions such as PTSD,” he said. “That’s what makes us interested in comparing and contrasting how these peptides work in the brain.”

McLean’s position as a freestanding psychiatric academic medical center makes it particularly suited to this research that encompasses five interrelated projects, said Chief Scientific Officer Kerry J. Ressler, MD, PhD. There are only a handful of Conte Centers across the U.S., named for a longtime Massachusetts congressman who was a strong advocate for federally funded research.

“The ability to have all aspects of psychiatry, including very basic science research, clinical research, and clinical treatment, provided in one place, focused on a targeted question, makes McLean uniquely positioned to address translational questions and to understand mechanisms, and then to apply those novel findings toward improved diagnosis, treatment, and prevention,” said Ressler.

Ressler noted that identifying the biological roots of PTSD and other related disorders, and applying the science to the care that individuals receive, will have enormous implications across the psychiatric field in delivering trauma-informed care across a person’s life span and within all diagnostic categories.

“This work has the potential to revolutionize the way in which clinicians deliver care to their patients,” said Ressler.

CONTE CENTER GRANT PROVIDES
OPENING TO UNDERSTANDING
THE ROLE OF SLEEP IN PTSD

DREAMING ABOUT PTSD



SD

TO SLEEP, PERCHANCE TO DREAM. EXCEPT WHEN THOSE DREAMS TURN INTO NIGHTMARES REPLAYING A TRAUMATIC EVENT FROM THE PAST.

That's why the study of sleep and circadian rhythm disruption is a central element of the 5-year, \$13.5 million research effort at McLean Hospital that hopes to better understand the roots of post-traumatic stress disorder (PTSD).

"Sleep problems are common to virtually every psychiatric illness," said Bill Carlezon, PhD, chief of the Basic Neuroscience Division and director of the Behavioral Genetics Laboratory at McLean. "People have nightmares. People can't sleep. One of the things that can happen when a person experiences these problems is they are tempted to self-medicate—by drinking or taking drugs—anything to make them feel relaxed."

What will make this project different is the parallel focus on the role of two neuropeptides, corticotropin-releasing factor (CRF) and pituitary adenylate cyclase-activating polypeptide (PACAP), that regulate the stress hormone cortisol and other biological processes that can affect the sleep process.

"IT IS IMPORTANT TO STUDY SLEEP AND TO UNDERSTAND HOW THESE STRESS PEPTIDES AFFECT IT, because sleep disruption

is not only a profound influence on PTSD itself, but it also plays a role in frequently co-occurring conditions like addiction, which compound the health problems and make them much more difficult to treat," he said.

PTSD is usually triggered by violence or abuse. Symptoms generally include nightmares and flashbacks as a person relives the trauma.

These symptoms alone do not indicate PTSD; they are not uncommon. But for 5 to 10% of the population, key symptoms can persist after a month, a sign of PTSD. Other indicators are problems like being constantly on edge, having trouble focusing, and feelings of low self-esteem.

DISRUPTED SLEEP CAN ALSO AFFECT THE CIRCADIAN RHYTHM, the 24-hour internal clock that controls the body's sleep/wake cycle running in the background of the brain, alternating between sleepiness and alertness. The biological clock is controlled in part by the hypothalamus, an area of the brain that also regulates hormones, including the stress hormone cortisol.

That interaction is a natural subject for Carlezon's lab, which aims to better understand how the environment

affects behavior and the biology of the brain.

"We're looking not only at how CRF and PACAP affect sleep, but also at the inverse: how problems with sleep affect these same peptide systems," he said. "We're doing some of the things that we know stress does to sleep, like changing patterns of REM and non-REM sleep, and looking at whether this increases or decreases the function of these peptides."

The working hypothesis is this represents a feed-forward cycle, where failure in a control system that should be providing balance instead creates an accelerating loss of control—a condition Carlezon likens to a runaway train.

"WE BELIEVE SLEEP DISRUPTION CAN BE THOUGHT OF AS A FORM OF STRESS, and we've shown that other forms of stress can cause an increase in the sensitivity of these systems," he explained. "In this case, the stress of not sleeping may amplify the stress of the previous trauma."

Carlezon has long dreamed of playing a role in bringing new treatments for psychiatric illness into humans. His first post-college job was in the drug discovery labs at Hoechst-Roussel Pharmaceuticals, which provided him with exposure to industry-scale approaches to the development of new therapeutic agents. He envisions a use for drugs such as CRF or PACAP blockers, which can dampen or block the brain effects of these peptides, offering an opportunity to restore balance, starting with a better night of sleep.

"CRF BLOCKERS SHOW PROMISING ANTI-STRESS EFFECTS IN ANIMAL MODELS, but for reasons that are not understood, they don't seem to work very well in humans with stress disorders," he said. "Our basic hypothesis is that CRF and PACAP work together and can

substitute for one another. And that's a potential explanation for why these

Carlezon, one of the lead researchers on the Silvio O. Conte Center for

our experiments in mice so we can track their sleep and biological rhythms for months at a time."

"IT IS IMPORTANT TO STUDY SLEEP BECAUSE SLEEP DISRUPTION IS NOT ONLY A PROFOUND INFLUENCE ON PTSD ITSELF, BUT IT ALSO PLAYS A ROLE IN FREQUENTLY CO-OCCURRING CONDITIONS LIKE ADDICTION, WHICH COMPOUND THE HEALTH PROBLEMS AND MAKE THEM MUCH MORE DIFFICULT TO TREAT."

And there are obvious inherent advantages in taking what is learned in animals and tracking those same responses in human beings.

single medications have not worked—when we block only one peptide system in isolation, the other simply takes over.

Translational Mental Health Research grant that combines five separate projects—involving species ranging from mice to humans—in pursuit of answers.

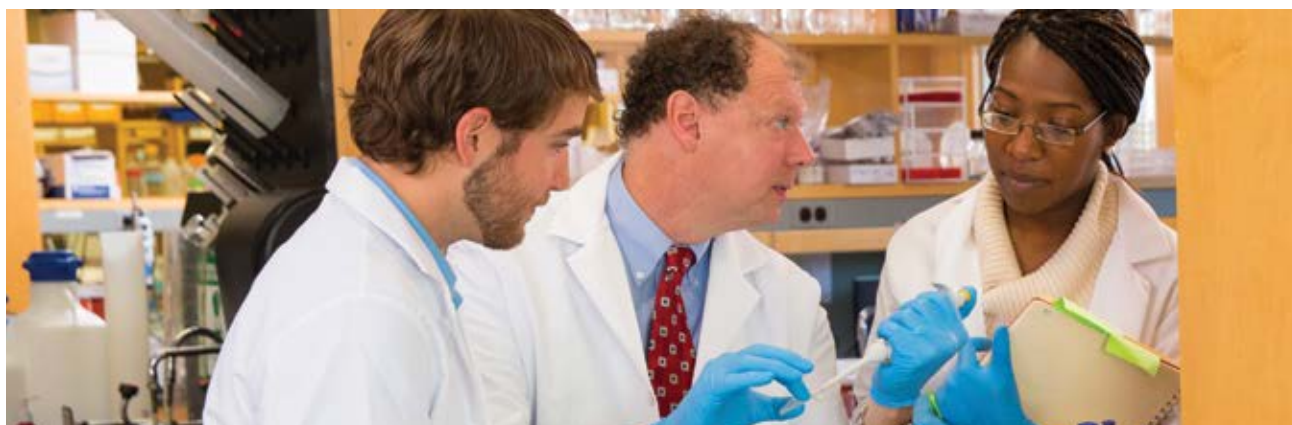
"SLEEP-RELATED ENDPOINTS ARE BECOMING INCREASINGLY ACCESSIBLE TO ALL OF US ON A REAL-TIME BASIS," he said. "Our smartphones and wearables, if we enable them, can keep track of the way we sleep and our biological rhythms, providing increasingly detailed readouts. Using these endpoints, research teams studying mice or humans can start comparing apples to apples, and our ability to do that is going to make the research done in the Conte Center inherently more valuable."

"THIS SUGGESTS TO US THAT WE MAY NEED TO BE BLOCKING CRF AND PACAP SYSTEMS at the same time, using two therapeutic approaches together instead of just one."

"Sleep is common to species ranging from jellyfish to flies to mice to humans. While there are obviously important species differences, sleep has the same basic attributes in all of them," said Carlezon. "We can set up

But research in animal models only takes researchers so far, noted

Top photo Bill Carlezon, PhD, right, is spearheading groundbreaking work looking at the role sleep plays in psychiatric illness. **Bottom photo** Kerry J. Ressler, MD, PhD, center, and his team are world-renowned for conducting innovative research on trauma-related psychiatric disorders.



USING MODERN MOLECULAR
RESEARCH TO BETTER
UNDERSTAND PTSD

RESEARCH TAKES BRA



INS

THE BRAIN— IT ONLY WEIGHS THREE POUNDS, AND 73% OF IT IS WATER.

But the remaining 27% is a dynamic computing machine that contains an estimated 100 billion neurons and has the capacity to generate 23 watts of power across synapses while awake.

THAT SYSTEM OF NEURAL CONNECTIONS IS WHAT SEPARATES HUMANS FROM OTHER ANIMALS—whose brains often weigh far more. And researchers at McLean Hospital are striving to understand how the molecules that power these circuits work—and how disorders are triggered when something goes awry.

Part of this work involves two neuropeptides that regulate the stress hormone cortisol—pituitary adenylate cyclase-activating polypeptide (PACAP) and corticotropin-releasing factor (CRF). McLean Hospital research focused on these neuropeptides is being supported by a 5-year, \$13.5 million grant from the National Institute of Mental Health.

“THESE ARE TWO OF THE BEST-UNDERSTOOD NEUROPEPTIDE SYSTEMS, YET THERE’S SO MUCH LEFT TO BE DONE,” said Kerry J. Ressler, MD, PhD, McLean’s chief scientific officer. “Nobody’s really brought to bear today’s powerful neurocircuit and other cutting-edge molecular approaches with the question of how these two molecular systems regulate the stress pathways, how they work in unison, and how they

complement or are redundant with each other.”

While Ressler’s lab focuses on these interactions in mice, colleague Sabina Berretta, MD, conducts parallel research with human brains from the Harvard Brain Tissue Resource Center, of which she is the director.

“The assumption that the same neural circuits and functions that we study in mice will directly translate into humans is being challenged,” she said.

“WE FINALLY HAVE THE TOOLS, ACROSS SPECIES, TO START UNDERSTANDING THE MECHANISMS OF HOW THE EMOTION CIRCUITS ARE WIRED AND ORGANIZED.”

“If I see this in a mouse, how will it compare to a human, and if I see this in a human, how do I use the mouse to understand it?”

The work is focused on the amygdala, the almond-shaped cluster of neurons that controls the fight-or-flight response, Ressler explained. He added that there are as many as 15 amygdala subregions with hundreds of different cell types that control not just fear but also addiction, aggression, and hunger.

Using genetic sequencing tools, Ressler’s lab compares different cells with different gene expression profiles and biochemical properties, in effect creating a map where each cell has

its own “zip code.” “Using a map metaphor, the early microscopy and histology tools of the past century allowed us to see a region of the brain like an entire continent,” he explained. “Recent molecular tools allow visualization of more discrete and small regions, perhaps at the level of states or counties on a map. Remarkably, the newest molecular tools for cell-level identification provide the ability to know what’s happening at each individual house.”

But the finding of obvious differences between human and rodent brains necessitates further testing of the hypothesis.

“THE ADVANTAGE OF USING POSTMORTEM TISSUE IS YOU CAN GO DOWN TO THE CELLULAR AND MOLECULAR LEVEL,” Berretta explained. “So, in that sense we can link the human imaging back to the other projects within the Conte Center by looking at the molecular aspects.”

The process begins with asking whether neurons that express CRF also express PACAP, and, if so, how they interact.

A SECOND COMPONENT OF HER RESEARCH WILL LOOK AT HOW THESE MOLECULAR SYSTEMS ARE CHANGED in donors who had post-traumatic stress disorder (PTSD).

“The first layer is where we simply look at expression of these molecules in different neural cells to understand how they interact,” said Berretta. “Where are they expressed in the brain? We need to look at circuits in humans that others will examine in rodents.

“One of the main hypotheses is there is a small group of neurons that express



The Brain Bank operates 24 hours a day, 365 days a year collecting postmortem human brain tissue that is used worldwide for research on psychiatric and neurodegenerative disorders.

CRF but also are receptors for PACAP. Those are primary suspects in co-regulating the stress response.”

These twin projects are all about correlating responses of humans with those of animals, Ressler explained.

“We can take a postmortem brain, and we can say ‘yes, in PTSD patients there

are different gene expression patterns.’ Or we can do human imaging and say ‘yes, people with these biomarkers have this brain activation pattern.”

“WE FINALLY HAVE THE TOOLS, ACROSS SPECIES, TO START UNDERSTANDING the mechanisms of how the emotion circuits are wired

and organized in the amygdala in a way that gives us real precision in understanding how they’re regulated with stress. Such progress could have profound effects on our ability to identify novel targets for treatment and intervention in PTSD, depression, and other stress-related disorders.”

TWO RESEARCHERS BROUGHT
TOGETHER BY ONE GOAL: IDENTIFYING
TREATMENT OF ANXIETY AND PTSD

TWO RESE
ONE GOAL

ARCHERS,



FIGHT OR FLIGHT. IT'S A BASIC RESPONSE TO A PERCEIVED THREAT IN ALL ANIMALS, FROM THE FLY TO THE HUMAN.

In complex vertebrates, including mammals, it is controlled by an almond-shaped cluster of neurons in the brain called the amygdala. This cluster regulates both pleasure and fear.

Scientists have long understood that brain chemicals known as neuropeptides are involved in regulation of stress responses, including a specific peptide known as corticotropin-releasing factor (CRF). Scientists at McLean Hospital are now looking at a related neuropeptide, pituitary adenylate cyclase-activating polypeptide (PACAP), and how the two may interact in controlling stress-induced anxiety. The goal of this research is to better understand generalized anxiety and post-traumatic stress disorder (PTSD) in humans.

"PACAP IS INVOLVED IN IMPORTANT BEHAVIORAL MECHANISMS essential for species survival," said Edward Meloni, PhD, one of the principal investigators at the Silvio O. Conte Center for Basic Neuroscience at McLean, funded by a grant through the National Institute of Mental Health.

"Animals need the stress and anxiety-related behavioral responses to survive. These behavioral mechanisms were picked up by evolution and can be

seen throughout the animal kingdom, including in humans. For humans, these adaptive mechanisms may become maladaptive, resulting in pathological states such as PTSD."

According to Vadim Bolshakov, PhD, a Conte Center Investigator, elevated CRF levels are frequently found in people with PTSD. While several potential treatments were tested but failed in clinical trials, researchers still believe targeting the CRF system could lead to effective therapeutics for some stress disorders, including generalized anxiety and PTSD.

What's new about the work of Meloni and Bolshakov is the focus on the interaction between CRF and PACAP.

"THE INTERESTING POINT IS THAT PACAP IS THE EXACT SAME NEUROPEPTIDE IN DIFFERENT ANIMAL SPECIES," said Meloni. "In mice, rats, dogs, cows, and humans, evolution has not changed the nucleotide sequence in even one amino acid. This suggests the peptide must be playing a very important role in species survival."

In humans, he continued, our hypothesis is that this same survival response is triggered when a person is exposed to a trauma-inducing natural disaster, terrorist attack, or school

shooting, for example, where one's life is in danger. But because humans are more evolved cognitively compared to animals, this response has the potential to do more harm than good.

"We believe that when a person is exposed to a life-threatening event, PACAP is released in the brain and may have a role in helping to hard-wire these indelible memories in the brain and/or sustain an anxious state," said Meloni.

WHILE SUCH A PROCESS MAY HAVE BEEN BENEFICIAL FOR SPECIES SURVIVAL, IN HUMANS IT MAY BE MALADAPTIVE, contributing to nightmares, flashbacks, or waking anxiety triggered by sights, sounds, and smells that remind the individual of the initial traumatic event.

Meloni, an investigator in the Behavioral Genetics Laboratory, and Bolshakov, the director of the Cellular Neurobiology Laboratory, are approaching the research from different angles. While Meloni introduces PACAP directly into animals, Bolshakov induces the release of the neuropeptide in specific brain regions using optogenetics, a relatively new methodology that involves the use of light to control brain cells that have been genetically modified.

In Bolshakov's experiments, a photosensitive protein called channelrhodopsin, derived from green algae, is delivered to the brain structures, orchestrating emotional and behavioral responses to stress. Brain cells expressing channelrhodopsin are then activated by blue light with unique precision.

Stimulating specific pathways in the brain, the researchers trigger the release of PACAP to see how it affects anxiety levels and how these effects are modulated by chronic stress. The Bolshakov lab also explores how PACAP and CRF interact in the amygdala and a small region of the

brain called the bed nucleus of the stria terminalis (BNST) to control anxiety.

“THERE IS EVIDENCE THAT BOTH NEUROPEPTIDES CONTRIBUTE TO THE DEVELOPMENT OF PATHOLOGICAL FEAR,” said Bolshakov. “Thus, their expression is enhanced in the brain when the subjects are experiencing fear-enhancing chronic stress.”

“IF YOU HAD A TREATMENT THAT COULD BE GIVEN IMMEDIATELY FOLLOWING A TRAUMA... YOU MIGHT PROTECT THOSE PEOPLE WHO ARE MOST SUSCEPTIBLE TO DEVELOPING PTSD.”

This enhanced PACAP- and CRF-mediated signaling in the brain is translated into changes in the functional interactions between certain brain regions, resulting in pathologically expressed fear, and thus often leading to psychiatric disorders.

“THE HOPE HERE IS THAT WE COULD EVENTUALLY COME UP WITH STRATEGIES FOR THE TREATMENT OF GENERALIZED ANXIETY AND PTSD, targeting specific parts of the brain circuitry controlling the development of pathological anxiety,” Bolshakov said.

Both researchers look at the expression

of PACAP and CRF before and after traumas to see whether that makes an animal more predisposed to developing PTSD.

That is done by measuring how much PACAP is in the brain during trauma and investigating the circuits that revolve around this PACAP/CRF release to, in effect, consolidate or enhance the memory of the trauma.

“Learning implicates memory consolidation,” Meloni said. “That is the hallmark of what is going on in PTSD patients, and we believe that memory consolidation of traumatic events is influenced by these peptides. Therefore, if we could control their actions, we possibly could come up with efficient treatments for PTSD.”

The work is also guided by the knowledge that there is an underlying predisposition to PTSD.

“We know many individuals that develop PTSD have early childhood exposures to abuse and to adverse kinds of living conditions that make

them more predisposed to develop PTSD,” Meloni said. “So, it may be because these stress-peptide systems are already dysregulated that there is an enhanced susceptibility to developing PTSD in the wake of a traumatic experience later in life.”

CLINICIANS KNOW THAT THE TRAUMA—THE CAR CRASH, EXPLOSION, OR SHOOTING—CAN LEAD TO THE FORMATION OF STRONGER MEMORIES.

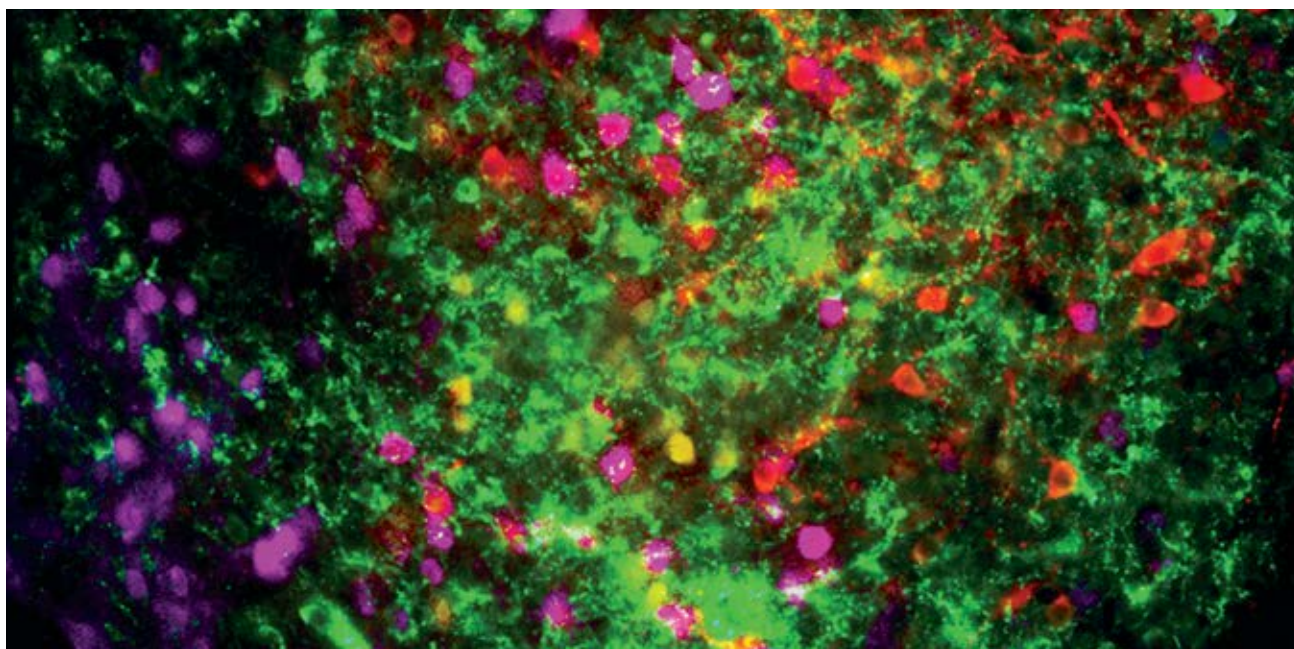
And Meloni said that when those consolidated memories are triggered by sounds or smell, it can result in a panic attack.

“It’s the memory hyper-consolidation of the cues surrounding the traumatic events that we think PACAP may be involved in,” he said.

Meloni was hopeful that his and Bolshakov’s work in animals could eventually apply to humans.

“We don’t yet know who is going to develop PTSD after exposure to a traumatic event, and only a small percentage of people will. But if you had a treatment that could be given immediately following a trauma—such as a drug that might block PACAP’s or CRF’s effects—you might protect those people who are most susceptible to developing PTSD.”

Composite image from immunohistochemical data (false-color labels) showing PACAP (green) innervation of the rat central nucleus of the amygdala in relation to corticotropin releasing factor- (CRF; red), PKCdelta- (PKCD; purple), and Arc- (yellow) expressing cells in this nucleus.



PTSD: MORE THAN TRAUMA

Studying stress-related factors in animals is an important first step in understanding what ails us and how to fix it. But that research only goes so far, particularly when these factors also confer risk for post-traumatic stress disorder (PTSD) in human beings.

As part of a 5-year, \$13.5 million grant through the National Institute of Mental Health, clinicians and neuroscientists at McLean Hospital plan to take what they've learned and apply that in a study involving men and women dealing with changes brought about by life-threatening experiences.

The research focus of Isabelle M. Rosso, PhD, director of the Anxiety and Traumatic Stress Disorders Laboratory, one of five projects of the Silvio O. Conte Centers for Basic Neuroscience, designed to explore PTSD by looking at the role of two neuropeptides in relation to stress.

"People used to think that PTSD was directly and solely caused by a trauma, particularly combat trauma, but we now know that constitutional risk factors play a major role," said Rosso. "Your genetics matter. Hormones and sex differences matter. Biology matters. Women are twice as likely to develop PTSD as men, and this is not entirely explained by social factors or differences in the types of trauma they experience."

The study aims to recruit an equal split of 230 adult men and women with PTSD to look at the physiology and neural underpinnings of stress and arousal. The goal is to relate measures of arousal to individual differences in the stress peptides corticotropin releasing factor (CRF) and pituitary

adenylate cyclase-activating polypeptide (PACAP). CRF and PACAP are involved in the normal and adaptive stress response, and they may be implicated in maladaptive responses that contribute to development of PTSD.

"It is normal to have an initial severe physiological stress response to a traumatic event, and for most people, this response abates during the first few months after trauma exposure," Rosso said. "A small proportion of people after a traumatic event continue to have very pronounced and debilitating symptoms for much longer and are ultimately diagnosed with PTSD. We want to understand whether variations in PACAP and CRF help explain individual differences in stress and arousal within people with PTSD."

The study will involve measuring PACAP and CRF from blood samples and examining how these neuropeptides relate to different ways to assess arousal.

"When a clinician diagnoses somebody with PTSD, one of the major types of clinical symptoms is hyperarousal," said Rosso. "People with PTSD are hypervigilant for reminders of their trauma. We can assess these clinical symptoms of hyperarousal using clinical interviews and see if they're related to PACAP and CRF."


"People used to think that PTSD was directly and solely caused by a trauma, particularly combat trauma, but we now know that constitutional risk factors play a major role. Your genetics matter. Hormones and sex differences matter. Biology matters."

Isabelle M. Rosso, PhD

It's also possible to measure the physiology of arousal using fear- and anxiety-causing laboratory tasks. The project will include laboratory paradigms of fear conditioning and dark-enhanced startle.

"If you're in a dark room and hear a loud noise, you'll probably startle more than if the room is





lit, and we can measure this as a change in your heart rate and other physiological reactions," she explained. "People with PTSD will have a greater dark-enhanced startle on average. So, we can measure their startle response, and ask whether variation in PACAP and CRF helps explain differences in these arousal responses."

The imaging will focus on brain regions and networks involved in fear and anxiety, including the amygdala, the almond-shaped cluster of neurons in the brain that plays a central role in fear. The study will combine measures of function, anatomy, and neurochemistry of these brain networks.

The study also will be the first to look at whether sleep problems relate to PACAP and CRF, she said.

"Sleep disruption is one very understudied component of hyperarousal in PTSD," said Rosso. "Over two-thirds of treatment-seeking people with PTSD report sleep problems. They have insomnia. They have nightmares. They have fragmented sleep."

Participants will be sent home with an actigraph to be worn on the wrist day and night to measure circadian rhythms and sleep. There will also be 3- and 6-month check-ins about their symptoms, particularly arousal.

"We want to see whether our baseline measures of PACAP, CRF, physiology, sleep, and imaging predict

later trajectories of symptoms—above and beyond clinical symptoms," she said.

Rosso said the interconnection of the projects under the Conte Center umbrella is important to the ultimate findings.

"PACAP and CRF are key regulators of stress and arousal across species, and all of the projects can inform each other," she said. "While researchers know through animal literature and more limited human findings that CRF and PACAP regulate the stress response, we don't fully understand what happens at the neurobiological level," she said. "If these processes are disrupted in PTSD, it could help us understand why some people have different responses to trauma and develop long-lasting disturbances in arousal."

LAUNCHING CAREERS WITH COVETED K AWARDS

K Awards, which are part of the National Institutes of Health (NIH) Research Career Development Awards, support the next generation of scientists focused on addressing the country's most pressing biomedical challenges. These awards serve to provide both salary and research for intensive, focused, and expertly supervised research training and career mentorship. K-level mechanisms are most often used to provide a foundation for successful transition into a newly independent research position or to support an individual's desire to gain extensive and expert training in a new field of specialty.

"Importantly, K awards have proven to allow early-career and new investigators to demonstrate their fundability and facilitate their progression on their academic career path," explained McLean Chief Scientific Officer Kerry J. Ressler, MD, PhD. "These awards comprise a unique opportunity for scientists in transition to independence to gain expert mentorship from proven NIH mentors and protected time and resources, which serve as a powerful launchpad for continued success in the biomedical sciences."

A Thoughtful Approach to Eating Disorders Research

The study of eating disorders tends to receive less attention than many other fields within psychiatry, despite the prevalence of these disorders and the impact they have on people's lives. Kristin N. Javaras, DPhil, PhD, is hoping her research will lead to more effective treatments for these conditions that are far deeper than simple lifestyle choices.



Kristin N. Javaras, DPhil, PhD

An assistant psychologist in the Division of Women's Mental Health at McLean Hospital, and initially trained as a statistician, Javaras said her career path was influenced by a desire to combine her analytic skill set with a fascination with psychological and psychiatric research. Collaborating with McLean clinical researchers James I. Hudson, MD, ScD, and Harrison G. Pope Jr., MD, MPH, to help analyze their data on eating disorders prompted her to add a degree in psychology and embark on a clinical and research pathway to better understand conditions such as anorexia nervosa, bulimia nervosa, and binge eating disorder.

As with many other behavioral health conditions, eating disorders have roots in stress and potential genetic preconditions.

"In the real world, stressors or negative emotions can precipitate an increase in eating disorder symptoms," she explained. "And in my own experience as a clinician, it can be hard to break the link between negative emotions and eating disorder symptoms. It is difficult enough for all of us to make changes when we're in a sort of neutral mood, but it

becomes even harder to implement a different strategy when you're upset."

Javaras' recent work is focused on how to better identify what areas of the brain are involved when someone has an eating disorder. Her hope is that by better understanding the brain circuits involved, the field will be able to develop treatments that are better tailored to the disorder and more effective.

"I'm interested in better understanding how eating disorders affect decision-making—for example, how that might differ in a person with an eating disorder from someone without an eating disorder," said Javaras. "Understanding how individuals with eating disorders make decisions is crucial for developing treatments that help people make everyday choices to promote recovery." One important feature of Javaras' research on decision-making is her focus on including people not just from the clinic, but people from the community, who may or may not be in treatment. That way, the research will be relevant—and hopefully helpful—to a broader array of individuals with eating disorders.

Exploring How Metabolism Affects Cognitive Function

The gastrointestinal system and the brain interact to play a key role in our health and well-being. This GI-brain axis goes far beyond the expression of "gut" feelings. It was this interaction that attracted Rachel A. Ross, MD, PhD, to psychiatric neuroscience.

"The GI system itself is kind of thought of as the second brain," she said. "It has a lot of the same neurotransmitters. It has a lot of the same neurons [that are also found in the



Rachel A. Ross, MD, PhD

brain]. Signals from the gut are sensed by the brain and can influence behavior.” Aided by a grant from the National Institutes of Diabetes and Digestive and Kidney Diseases, she is now exploring the relationship between hunger and cognitive function as an assistant neuroscientist in the Neurobiology of Fear Laboratory and a staff psychiatrist at McLean Hospital.

“There is a lot of work that shows that people have abnormal responses to feelings of hunger or feelings of fullness, depending on which side of the spectrum you’re looking at,” she said. “And that is probably related to the biological signals that come from the gut and are interpreted by the brain.

Working with mice and using cues gleaned from her clinical practice, Ross is building on existing research that found that an impairment of cognitive function is associated with a reduction in activity in the medial prefrontal cortex.

Using a genetic model that enables her to home in on neuropeptides—the small protein-like molecules used by neurons to communicate with each other—she is exploring what drives cognitive function related to food intake behavior and metabolism.

“The receptor for this neuropeptide system is found in numerous regions throughout the brain, and what it’s doing is not well understood,” beyond the fact that it responds to two neuropeptides that have opposite effects on food intake, she said. In particular, the search is to understand what role it might play in decision-making.

The growing subspecialty of psychiatric neuroscience aims to better understand how biological and cognitive factors interact to develop targeted treatment of psychiatric illness, such as anorexia, that often lead to medical complications or suicide.

“In the past, it was hard to appreciate how the study of the brain in a biological manner might actually help us understand what was happening in that person,” she said. “But now, with newer tools, that’s becoming more accessible, so I think this is a field that has been growing and hopefully will come up with some really useful direction for improving how we understand psychiatric illness.”

Can Big Data Tell Us Why PTSD Exists?

Is there a genetic predisposition to post-traumatic stress disorder (PTSD)? Nikolaos P. Daskalakis, MD, PhD, director of the Neurogenomics and Translational Bioinformatics Laboratory at McLean Hospital, thinks the answer is yes. And he is committed to analyzing lots of data to confirm it.

Daskalakis is combining traditional medical training in behavioral neuroscience and neuroendocrinology with systems biology and “big data” computing to explore whether a person’s genetic makeup can play a role in the development and treatment of PTSD. This is a condition that affects up to 8% of the population at some point in their lives.



Nikolaos P. Daskalakis, MD, PhD

The principal factor of PTSD was and remains a traumatic event. But, said Daskalakis, “a genetic predisposition to psychiatric disease has long been recognized in schizophrenia and is now coming into focus for PTSD.”

Researchers can be hampered by difficulties in defining PTSD. Are all PTSDs the same? Since there are differences in trauma types, are there differences in PTSD types? Is PTSD caused by a car accident different from PTSD caused by a terrorist act?

The search for an answer to that question is at the heart of statistical genetics, a subspecialty that has developed over the past 20 years. It uses data gleaned from traditional medical biomarkers and now, increasingly, integrates data from postmortem brain samples.

“There is something in the genetic makeup of individuals, the genotype that people are conceived with from day zero or some epigenetic state they partially inherited or developed as they were growing, that could be positive or negative,” Daskalakis said.

“The genomic makeup will play out in how they will immediately respond or if they will be the ones who have the chronic sequelae of trauma-related symptoms.”

The genetic link to schizophrenia was established as researchers gained enough data to identify specific loci, or fixed positions on the chromosomes linked to the disease. Similar work on PTSD is underway using large genotype collections of disease, such as the PTSD working group of the Psychiatric Genetics Consortium, co-led by Kerry J. Ressler, MD, PhD, McLean's chief scientific officer.

Expanding the scope of the data analysis to integrate functional genomic data derived from brain tissues, such as those collected by the Harvard Brain Tissue Resource Center, involves bioinformatic modeling and novel techniques of machine and deep learning using improved computing power.

Today's statistical geneticists are trying to identify "genetic or genomic biomarkers that could help understand how many different types of PTSD exist," he said, a discovery that could open the possibility of clinical trials, which haven't been effective to date.

The multidisciplinary work involves the Harvard Paulson School of Engineering and Applied Science, the MIT Computer Science and Artificial Intelligence Laboratory (CSAIL), and the Broad Institute.

Believing Survivors of Childhood Abuse Is a Global Ethical Issue

Nearly two-thirds of people in the United States have experienced at least one traumatic event during childhood. Of those, close to 10% will go on to develop post-traumatic stress disorder. A subset of those individuals, upwards of 3 million people in the U.S. alone, experience a particular type of post-traumatic coping response called dissociative identity disorder (DID). DID, in particular, is associated with prolonged and severe childhood abuse and neglect, typically at the hands of caretakers.

Yet "the existence of DID and its associated symptoms have long been misunderstood and at times ignited controversy," said Lauren A.M. Lebois, PhD, a cognitive psychologist and neuroscientist in the Dissociative Disorders and Trauma Research Program and Neurobiology of Fear Laboratory at McLean Hospital. She is working on research that tracks brain responses through functional magnetic resonance imaging (fMRI).

"Most treaters don't assess for DID, and if someone happens to report these types of symptoms, some treaters may discount or even disbelieve them. This doubt lays the groundwork for a vicious cycle of stigmatization, misdiagnosis, and delayed healing."

Dr. Lebois and her colleagues hope that by elucidating the neurobiology of DID, they will help destigmatize the disorder so that people can access the treatment they need. The research supported by her National Institute of Mental Health K award proposes to do just that by studying dissociative symptoms that are a hallmark of DID.

"One of the ways symptoms manifest for people with DID is sometimes when they look in the mirror, their reflection feels off or strange in some way. And sometimes it can feel like it's someone else looking back at them in the mirror—even though they know it must be their own reflection."

To study these symptoms, Dr. Lebois and her colleagues have designed a novel task in which participants with DID and a control group of people without DID are shown pictures of their own face while they measure brain activity through fMRI.

Their research to date has found that for people with DID, seeing their own face doesn't elicit feelings of familiarity like it does for control participants. Preliminary fMRI findings support this, indicating that a number of brain regions that are typically active when someone looks at their own face aren't active in someone with DID.

While expanding existing treatment options is a long-term goal, Lebois said the more urgent goal of her work is to raise awareness of DID—and the role of childhood trauma as a cause.

"It's troubling—a global ethical issue, actually—that the most vulnerable people in our society, children, have these experiences of abuse and neglect. And, on top of that, as adults they can't access the mental health treatment that would help them because there's so little understanding in the medical, clinical, and lay communities."



Lauren A.M. Lebois, PhD



A GLIMPSE INTO THE FUTURE

JUSTIN T. BAKER THINKS IT'S TIME
FOR PSYCHIATRY TO ADAPT TO A CHANGING CULTURE
AND A YOUNGER COHORT OF PATIENTS

MOVING TO A MORE DATA-DRIVEN PRACTICE

poses a challenge in a health care system that is moving toward what is thought of as a more cost-effective model of providing the right care in the right place at the right time, one that may no longer focus as heavily on direct contact in a brick-and-mortar environment.

“Humans who are suffering don’t want to be alone all the time,” said Justin T. Baker, MD, PhD, scientific director of the Institute for Technology in Psychiatry and director of Functional Neuroimaging and Bioinformatics for the Schizophrenia and Bipolar Disorder Research Program at McLean Hospital. “So, the idea here is not to just push people into remote monitoring scenarios where they never see another human.”

“We can either choose the glass and metal future, or we can choose the grass and mahogany future,” he continued. “We have to be careful that the future that we generate for our patients is the one we’d want. I chose the grass and mahogany. What I like about McLean is that while it has 200 years of history behind it, the hospital continuously strives to embrace and set the bar for a modern approach to patient care.”

Baker pointed out that McLean was established in 1811 to promote the ethical treatment of individuals with mental illness. “That is something McLean proudly continues to do today, but we also understand that the need for our services is greater than ever, and not everyone can physically come to our campuses for care. That’s where we blend tradition with the future.”

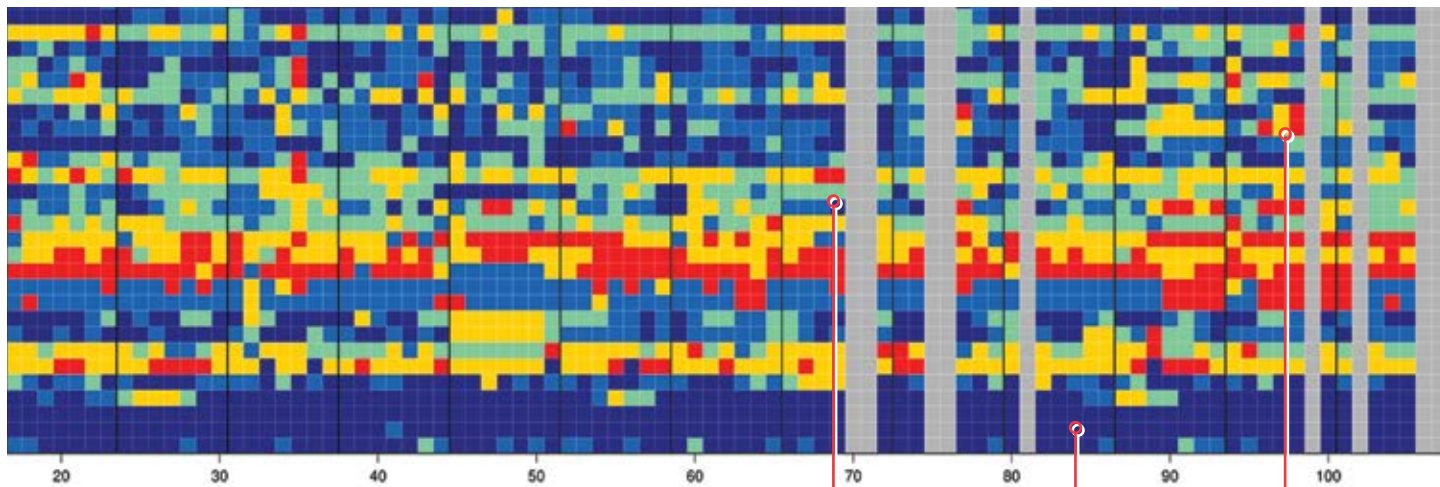
The start of that shift can be seen in MultiSense, an artificial intelligence program developed at Carnegie Mellon University, and the SimSensei virtual interviewer named Ellie. This AI model draws on techniques taught to psychiatry residents by McLean’s Elizabeth Liebson, MD, and relies on methods used by psychiatrists at inpatient programs.

But a virtual interviewer will only be effective if it serves as an extension of—and not as a replacement for—the in-person encounter, Baker stressed.

An interim step is underway in a just-launched study. Using data and information gleaned from both devices and in-person encounters, researchers will track many aspects of daily lives, from work and leisure patterns to interpersonal interactions and what someone is doing at those moments.

“IT’S A UNION OF ALL OF OUR METHODOLOGIES INTO ONE MASSIVE STUDY of more than 100 people who let us take a bird’s-eye view of their life over a year or so, during which they’re going to go through all kinds of ups and downs,” said Baker. “We want to sort of be there with them and experience that journey alongside them as much as possible.

“Say that person has a smoking habit. Let’s zoom in to them taking a single drag of a cigarette and zoom out to a year to see every single drag of a cigarette. Where did it happen? When did it happen? Who were they with? How was it influenced by their treatments or stress? Can we use these data to unpack a manic episode and understand at the level of an individual how it emerged from a series of events? We get



The longitudinal graph above represents how an individual feels over the course of time. Each day, the survey participant is asked to assess certain aspects of their overall mood, such as “energetic,” “hostile,” “irritable,” or “happy.” Hotter colors represent higher responses (e.g., more energetic), and cooler colors represent lower responses.



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to see all of these things unfolding in the real world and really understand them for the first time.”

THE TRACKING DATA WILL BE COMBINED WITH MONTHLY CHECK-INS where the patient and clinician will review the data along with audio and video recordings. That is in keeping with the fact that care requires basic flesh-and-blood contact beyond technology.

“Why do we need in-person contact? Because without it, the clinician may be missing key information when it matters most,” he said.

While chatbots can serve a useful purpose, particularly with the growing reliance of younger people on text-based interactions, a problem remains.

“What happens when that person gets really sick? Do we have her see a specialist? How do you get that person triaged?”

The move to a more technology-based practice will also require stronger privacy and ethical safeguards. The growth of blockchain technology and a recognition that patients, not health care systems, own the data will help on the privacy front.

“YOU’LL BE ABLE TO SHARE [DATA] WITH THE RESEARCHER, with your clinician, in a way that they don’t have otherwise,” Baker said. “When you come in for your visit, there will be an expectation that you’re being recorded, and there’s data entering your chart, and it will get integrated with your medical record.”

Baker acknowledged ethical issues are “uncharted territory.”

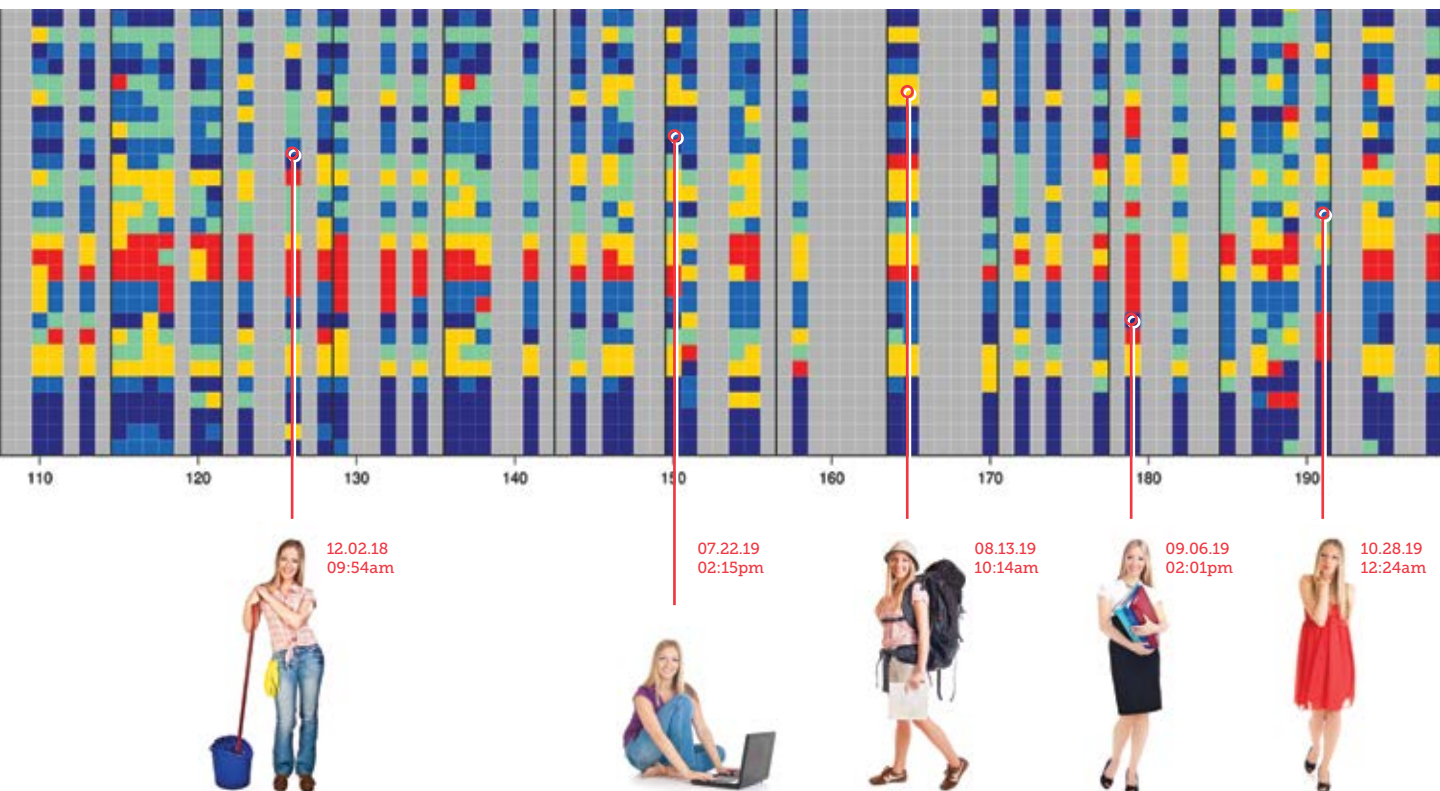
“I think we’re in that moment now where we are starting to look for the first time at what it actually means to be human in a really granular way,” says Baker, “and we’re watching people with these sensors and cameras to understand that condition in ways that no one has ever done before. And people start to say that’s creepy. And it kind of is. But people opt in to this level of scrutiny.”

BAKER DREW UPON AN UNUSUAL COMPARISON to frame how patients and clinicians should view behavioral health in the future.

“What the dental industry was able to do was convince the public that hygiene mattered,” said Baker. “They marketed the toothbrush. They marketed the 6-month checkup from age 2 on. And now we all just do that. Insurance companies pay for it, because they know that actually it’s cheaper than having to pay the oral surgeon.”

Ultimately, he said, the challenge involves merging the Hippocratic Oath and humanist medicine with a radical re-envisioning of what mental illness is.

“We’re not just going to assume that the doctor knows best,” said Baker. “You could never design a system to do what a doctor can do anyway. We’re going to try to be humbler and let patients guide us toward solutions that work for them, even if it’s not always great for the doctor or the system.”





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McLean Hospital is pleased to offer an intensive course on PTSD, bringing together some of the foremost authorities in the field with a shared goal of providing hope to patients and families by informing clinicians of the most cutting-edge, research-informed treatments.

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