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Applying Mindfulness Approaches to Stress Reduction

Stress. There is no way to avoid it in today's fast-paced world. There are, however, ways to better manage stress and anxiety, according to **Susan Evans, PhD**, Professor of Psychology in Clinical Psychiatry, Director of Education in Psychology, and Director of the Cornell Cognitive Therapy Clinic at Weill Cornell Medicine. Dr. Evans, who is an expert in the cognitive behavioral treatment of anxiety and mood disorders, also specializes in stress management, and specifically Mindfulness Based Stress Reduction (MBSR).



Dr. Susan Evans

Dr. Evans became interested in MBSR in the late 1990s and completed an internship in 2000 at the Center for Mindfulness at the University of Massachusetts Medical School under the direction of Jon Kabat-Zinn, PhD, creator of MBSR who

originally developed the program as an aid in pain relief. Dr. Evans then established the Mindfulness Based Stress Reduction Program at NewYork-Presbyterian.

"Mindfulness is best defined as moment-to-moment non-judgmental awareness; it's about training your mind to be completely present, right here, right now in the moment," says Dr. Evans. "The way we do that is through certain formal meditation practices."

Mindfulness meditation is steeped in the tradition of Theravada Buddhism, Zen practices, and yogi practices, explains Dr. Evans. "Dr. Kabat-Zinn and others have done a lot to westernize the practice; for example, removing any religious language so that it is very palatable. It is

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Tracing and Tagging Memories: Science Fiction Becomes Science Fact

Toward the end of the February 10, 2016 episode of PBS's NOVA, *The Memory Hackers*, **Christine A. Denny, PhD**, Assistant Professor of Clinical Neurobiology in the Department of Psychiatry at Columbia University Medical Center, places a small mouse gently into a lidless, transparent plastic box with a hard, white plastic floor, surrounded by bright lighting. The mouse huddles in a corner.

Dr. Denny then turns a key on a small box nearby sending a laser light through two narrow fiber-optic tubes attached to the mouse's skull, aimed at a few hundred cells in its brain. The day before, these exact neurons had been tagged with the mouse's experiences – as it was having them – of soft, earthy bedding, dark surroundings, and a plastic rock cave to hide under. The mouse's perception in the plastic box is now rife with this specific stimulated memory. The mouse moves from the corner, sniffing and exploring. He grooms

himself, a clear sign of feeling safe, and peruses the entire landscape of this moments-ago adverse environment. When Dr. Denny turns off the laser input, the mouse retreats to the corner. When she turns the memory back on, he ventures forth again. With control of the laser light, she can turn his particular memory on and off.

Dr. Denny compares this startling demonstration, including her own initial sense of surprise, to the science fiction of movies like *Eternal Sunshine of the Spotless Mind* or *Inception*. "The first time we did it," she tells NOVA, "we didn't believe it. But when you see inside of the brains of these mice," she says, as NOVA shows images of the specifically tagged neurons in phosphorescent yellow-green on Dr. Denny's computer screen, "and then to think that you are only manipulating those cells and changing the behavioral output of the animal,

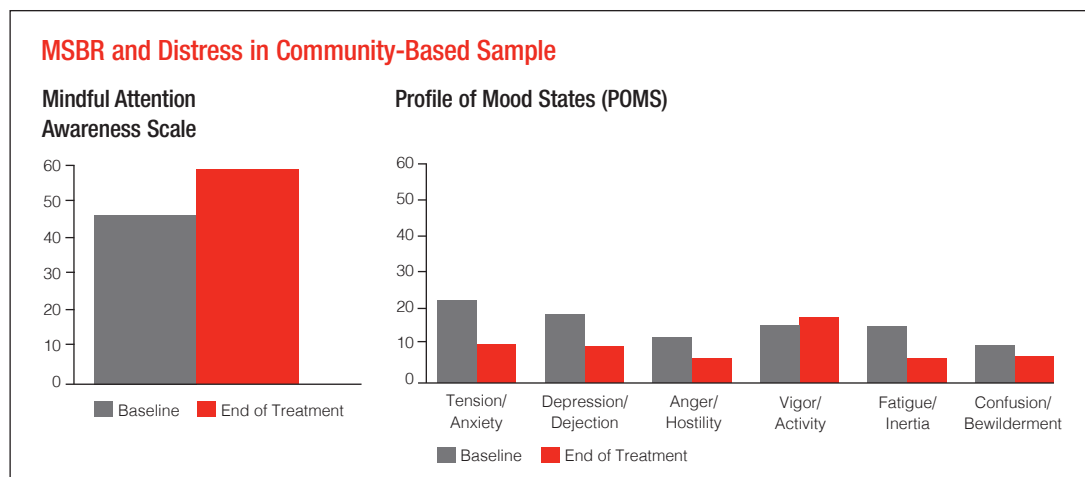
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Applying Mindfulness Approaches to Stress Reduction (continued from page 1)

not about religion, but it is based on this eastern contemplative tradition.”

Dr. Evans’s MBSR program is an eight-week course, conducted in the spring and fall, primarily for people in the community – working professionals, students, or at-home parents, for example, who are interested in learning how to better manage the stress and anxiety in their lives.

“These are individuals who are not necessarily coming in with any clinical diagnosis of anxiety or depression,” says Dr. Evans. “But I do give them measures of mood states that have various subscales, including anxiety, tension, depression, and fatigue. They score higher than a normative sample that the scale is based on, so it suggests that there is a lot of worry out there. These people are functioning well, but they actually are mildly symptomatic in terms of mood and anxiety.”



Dr. Evans screens participants with the Mindful Attention Awareness Scale designed to assess core characteristics of mindfulness, informed by a sensitive awareness of what is occurring in the present. The scale is comprised of a collection of 15 statements about everyday experience, such as “I do jobs or tasks automatically without being aware of what I’m doing,” with a scale of one (almost always) to six (almost never). Higher scores reflect higher levels of dispositional mindfulness.

The MBSR program consists of formal meditation practices that include body scan meditation in which one focuses on different parts of the body as a way to be present. “We also employ sitting meditation where the primary focus is on the breath. Not changing or manipulating breath in any way, but having the breath as a place to come back to when your mind goes off,” says Dr. Evans. “The other practice is gentle hatha yoga, focusing on the pose and the breath as an anchor to which to return when your mind wanders.”

The program requires a significant time commitment. “There is daily homework and that includes practicing meditation about 30 to 45 minutes each day,” notes Dr. Evans.

Healthcare providers have found the program beneficial as well, says Dr. Evans. “We also conducted a pilot study with medical students here at Weill Cornell Medicine who went through the mindfulness course. They appeared to really enjoy it and benefit with reductions in stress and improved mood. They also said they would like to have shorter, 10-minute meditation practices.”

More recently, Dr. Evans has been examining the constructs of self-compassion and acceptance and how these factors may play a mediating role in the positive findings of MBSR. “We know that from the studies we’ve done here and elsewhere that people experience reductions in anxiety and improved mood and well-being pre to post the eight-week mindfulness sessions,” says Dr. Evans, who conducted an earlier study on MBSR and distress in a community-based sample of 14 participants (see graph at left). The results suggested that MBSR appeared to be associated with a reduction of distress and increased awareness of everyday life experiences.

“A question we are exploring now is whether self-compassion and acceptance mediate the positive effects of mindfulness training,” she says. “Self-compassion involves adopting a kind and understanding stance towards ourselves, as well as taking the perspective that suffering and experiences of personal shortcomings are universal.

Acceptance entails adopting a balanced approach to negative emotions so that feelings are neither suppressed nor exaggerated.

“Early research in the usefulness of MBSR conducted by Dr. Kabat-Zinn centered on its effect on pain and then anxiety disorders,” says Dr. Evans. “Since then there has been a burgeoning of research and interest in the techniques in the last 10 years.”

In September, Dr. Evans presented research on MBSR in Stockholm, Sweden, at the European Association of Cognitive Behavioral Therapy. Her study, which is under review for publication, was based on data collected on 42 community-based individuals, ages 25 to 74, who completed the eight-week MBSR course. Overall the participants benefited in decreased mood symptoms, and increased mindfulness, acceptance, and self-compassion.

“More and more MBSR is becoming enormously popular,” says Dr. Evans. “When I started the program here at NewYork-Presbyterian, it was relatively new. People weren’t so sure about it, but today it has become part of mainstream health care.

“There’s much more interest now in teaching these skills to young children,” adds Dr. Evans, “and so we are seeing things like mindful eating being taught in schools. I think we’re going to see more of that in the future.”

Reference Article

Evans S, Ferrando S, Carr C, Haglin D. Mindfulness-based stress reduction (MBSR) and distress in a community-based sample. *Clinical Psychology and Psychotherapy*. 2011 Nov-Dec;18(6):553-58.

Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. *Journal of Anxiety Disorders*. 2008 May;22(4):716-21.

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Tracing and Tagging Memories: Science Fiction Becomes Science Fact *(continued from page 1)*

that's science fiction." Dr. Denny knows, however, this remarkable tagging of the neurons of a specific memory is very much science fact, and predicated on the work of more than 10 years at Columbia.

Memory Defining Questions

Dr. Denny is interested in the molecular mechanisms underlying learning and memory and she and her research team have developed a novel technique to label the cells that encode individual memories in the brains of mice. They are then able to indelibly tag these neurons using fluorescent molecules.

"In humans, we can look at brain regions of activity using fMRI or a number of methods; in an animal model you can look at activity based on gene expression," she explains. "While this can tell us what cells are active when you learn or remember something, there wasn't a tagging system available where you could permanently label one memory, then wait for the lifetime to occur or disease to set in, and then look at what happened to that memory. Therefore, we created these mice to allow for an indelible tag of one particular memory. We look at cells that are active during learning and cells that are active during remembering information learned. And then we look for overlap. And if that cell is active at both time points, we call that a memory trace or an engram."

Dr. Denny's lab was the first to inhibit the specific cells that are activated when something aversive is learned. "When we put the animals back into the aversive context, we could shut off the cells of very small subsets – a few hundred cells or less – and we could block retrieval of that fear memory."

An article published in 2014 in *Neuron*, for which Dr. Denny is lead author, examines how the permanence of memory traces or engrams permits remarkably specific location of memory in the hippocampus (HPC) and begins to examine the vicissitudes of experience and stress on the development of the network of neurons involved in learning and memory. The study utilized the immediate early gene (IEG) *Arc* to understand how a memory trace is formed and retrieved in the HPC under a number of circumstances. The research team designed the *ArcCreER^{T2}* bacterial artificial chromosome (BAC) transgenic mice to test this hypothesis not just on a short timescale, but also indefinitely. "We were able to compare cells activated during the encoding of a memory to cells activated during the expression of that memory," notes Dr. Denny.

Their hypothesis "that the cells reactivated during expression of memory are a component of memory traces" finds its evidence in the mouse dentate gyrus (DG) and CA3. The researchers showed that, "mice re-exposed to a fear-inducing context froze more and had greater percentage of reactivated cells in the dentate gyrus (DG) and CA3 than mice exposed to a novel context." They also corroborated that the differences disappeared over time in keeping with the observation that memories become generalized. Additionally, silencing DG or CA3 cells that were recruited during encoding of a fear-inducing context prevented expression of the corresponding memory.

"Arc is definitely in humans," Dr. Denny says, in connecting her research in mouse models to the clinic. "And it's been implicated in a number of diseases, like Alzheimer's and others." Dr. Denny and her colleagues have created mouse models to investigate what happens to hippocampal memory traces in normal, aged, and Alzheimer's diseased mice. "Is the problem that you just do not



Dr. Christine A. Denny

remember as well or is the memory there and not being accessed correctly? When you have a tagging system, you can answer those types of questions. Without the tagging system, you can basically only determine global brain activity at any given time point, but not whether the cells were active at an earlier time point.

"A model that is permanent, that lets you have a tag forever, can start to get at these questions that occur with disease onset," adds Dr. Denny. "The nice thing about this mouse model is you can breed it with any other disease model to study how that disease impacts memory. This enables you to visualize what is going on before and after disease progression and then to manipulate it to answer very specific questions. We hope to identify the altered memory circuits and how to manipulate them in order to improve memory retrieval seen during cognitive aging."

Most recently, Dr. Denny and her colleague, **René Hen, PhD**, Professor of Pharmacology (in Psychiatry) at Columbia University Medical Center and Director, Division of Integrative Neuroscience, New York State Psychiatric Institute, have received a substantial grant to perform whole-brain imaging. "Instead of looking at just individual parts of the brain to identify which cells are part of a memory trace, we can now image the entire brain and get a memory trace map across all circuits of the brain," says Dr. Denny. "I'm a clinically inspired scientist. My philosophy is that you use mouse models to gain insight or information on disease processes on a level that wasn't previously possible before. And then use that information to better design future studies that could impact disease progress or understand how it occurs in the first place. If you do that, you really can make an impact on bringing your work from pre-clinical models back into the clinic."

Reference Articles

Cazzulino AS, Martinez R, Tomm NK, Denny CA. Improved specificity of hippocampal memory trace labeling. *Hippocampus*. 2016 Jun;26(6):752-62.

Denny CA, Kheirbek MA, Alba EL, Tanaka KF, Brachman RA, Laughman KB, Tomm NK, Turi GF, Losonczy A, Hen R. Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis. *Neuron*. 2014 Jul 2;83(1):189-201.

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