

WE'RE ALL STRESSED: HOW CAN SCIENCE HELP?



George Slavich recalls the final hours he spent with his father. It was a laughter-packed day. His father even broke into the song ‘You Are My Sunshine’ over dinner. “His deep, booming, joyful voice filled the entire restaurant,” says Slavich. “I was semi-mortified, as always, while my daughter relished the serenade.”

Then, about 45 minutes after saying goodbye outside the restaurant, Slavich got a call: his father had died. “I fell to the ground in a

puddle of shock and disbelief,” he says.

Slavich recognized the mental and emotional trauma he was feeling – and could imagine how it would affect his health. He studies stress for a living, after all. Yet even after he brought up his concerns, his health-care provider didn’t evaluate his stress.

“If stress isn’t assessed, then it isn’t addressed,” says Slavich, a clinical psychologist at the University of California, Los Angeles. “The experience highlighted a paradox between what I know stress is doing to

the brain and body, and how little attention it gets in clinical care.”

Decades of research have shown that, although short bursts of stress can be healthy, unrelenting stress contributes to heart disease, cancer, stroke, respiratory disorders, suicide¹ and other leading causes of death. In some cases, prolonged stress drives the onset of a health problem. In others, it accelerates a disease – or induces unhealthy coping behaviours that contribute to chronic conditions².

Stress also seems to be on the rise. It

Improved stress assessment and tailored interventions could give clinicians the tools they need to fend off lasting damage.

By Lynne Peeples

increased globally during the recession of 2007 to 2009 and the COVID-19 pandemic, says David Almeida, a developmental psychologist at Pennsylvania State University in University Park, who studies historical shifts in stress as well as everyday stressors. Polls show that globally, including in the United States, stress hasn't gone back down to previous levels.

"Any time there is uncertainty in society, we see increases in reports of stress," says Almeida. Uncertainty can ramp up our responses to stressors that are usually minor, he says: "Being stuck in traffic might make you more upset than it did before."

Although people tend to be aware of their stress, they often don't know what to do about it. A physician might recommend leaving a stressful job, engaging in talk therapy or eating and sleeping better – but those options are not always possible. In fact, many of the individuals who face the greatest stressors also face the greatest barriers to treatment. What's more, some people take pride in how many demands they can juggle, wearing stress like a badge of honour, says Slavich.

He, Almeida and other researchers are trying to change the current thinking. Emerging assessment tools, along with basic advances in stress science, now make it possible to answer questions such as 'When does good stress turn bad?' and 'How can we intervene effectively?' An improved understanding of stress, says Slavich, could "fundamentally transform health care".

Good versus bad stress

Sources of stress run the gamut: a high-stakes presentation at work, a disagreement among friends, trauma from military conflict, living in poverty, structural racism, divorce, a lost job – or a lost loved one.

When the body perceives a threat, stress hormones, including cortisol, flood the bloodstream. Muscles tense and blood sugar levels rise. The heart beats faster and stronger, and blood vessels dilate, shuttling extra oxygen through the body to help you think and move quicker. The immune system is put on call for rapid healing and recovery.

This fight-or-flight response has, over millennia, helped humans to survive. But it

didn't evolve to cope with traffic, cyberbullying, credit-card debt and the countless other stressors of modern life.

"There is an evolutionary mismatch happening right now," says Almeida.

Issues arise when the body fails to control the on-off switch, says Wendy Berry Mendes, a psychologist at Yale University in New Haven, Connecticut. Stress becomes problematic if the body overreacts to situations that are not life-threatening, anticipates a stressor too soon or dwells on negative feelings after the stressor has passed – or if a source of stress sticks around for too long. When cortisol and the sympathetic nervous system are dialled up for extended periods, good stress can turn bad. But how would someone know when the line is crossed?

Stress assessments tend to rely on self-reported symptoms, such as anxiety or trouble sleeping, plus, in some cases, on measurements of blood pressure, cortisol levels or heart rate. These tools aren't always sufficient. An elevated cortisol level or heart rate, for example, could be explained by exercise or "that cup of coffee you just had", says Almeida.

Blood pressure, cortisol and heart rate also rise and fall naturally throughout the day. The timing of the measurement matters, as do patterns over time. Mendes says she is most confident in cortisol measurements that are taken approximately 30 minutes after waking, when a healthy person should experience a strong spike. Heart-rate variability, a measure of the natural fluctuation in the time between beats, is also much more informative as to how the body regulates stress than is the heart rate itself, she says.

Access to many more types of measurement might offer a fuller picture, say researchers. Nearly the entire body reacts to stress, including the nervous, respiratory, digestive, cardiovascular, immune, circadian and endocrine systems. In a study that has not yet been peer reviewed, Slavich and his colleagues found that the expression of more than 1,500 genes, especially those involved in inflammation and antiviral responses, can change after a person is socially stressed for as little as 10 minutes³.

With this complex cascade in mind, Slavich and his colleagues are investigating a broad array of self-reported measures, including past stress and trauma exposure, as well as data on neurotransmitters, hormones, genetics, gene expression, gut bacteria, inflammatory markers, glucose levels, lipid function and metabolites. These data are now easier to obtain, often with affordable at-home tests.

The COVID-19 pandemic spurred the creation of simple-to-use devices to collect blood, saliva and stool samples. In parallel, there are increasingly small and powerful wearables that can continuously assess physical activity, sleep, heart rate, heart rate variability, vestibular balance and galvanic

skin response. Sensors under development aim to detect real-time levels of cortisol and other stress hormones through sweat⁴. Meanwhile, researchers are designing ways to gauge blood pressure when people are on the go.

There are limitations to the wearables currently on the market, says Mendes: "Many physiological measures that wearables can detect are simply easy to obtain rather than being the most informative about stress or health." Still, optimism is high that measures that can be taken quickly and with little or no effort will help people to become more aware of their stress level and will advance stress science.

The influx of data could help researchers to understand how stress contributes to long-term health problems, as well as offering guidance in the clinic. Currently, there are no clinical cut-offs that indicate harmful stress, says Slavich. By contrast, a health-care provider concerned about cardiovascular disease, for example, can measure levels of C-reactive protein, a marker of inflammation, to determine whether a person is at an elevated risk and whether they'd benefit from further testing and treatment. "If you are going to transform clinical care and give health-care providers and patients a target to move towards, that's a first step," he says.

For harmful stress, Slavich anticipates that a more robust and continuous stress score, derived from a combination of signals, might be needed.

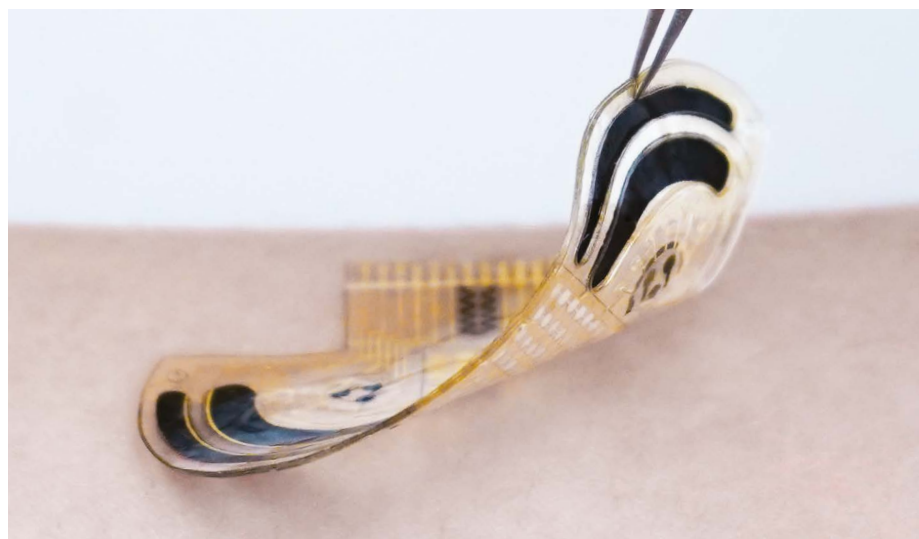
Stress gets personal

The good news is that a variety of interventions are already available, and more options are on the horizon.

Robust clinical trials show that cognitive behavioural therapy, breathing exercises, social support, exercise and time spent in nature can fight bad stress by altering how a person thinks, how they act and how their body responds to stress. Cognitive behavioural therapy has been shown to reduce how much people dwell on negative feelings after a stressor, for example, as well as helping a person to reframe their perception of an upcoming stressful event. Last year, a meta-analysis of techniques for reframing stress concluded that they can provide a small boost in performance on a range of tasks, notably those that involve social evaluation, such as giving a business pitch⁵.

There are other tools that can help a body overwhelmed by stress. Beta blockers, for example, can be prescribed to tamp down the sympathetic nervous system as needed. Anti-inflammatory drugs can calm an immune system that remains activated after a bout of stress. Even omega-3 fatty acids can buffer the stress response and reduce inflammation.

Part of the challenge going forward will be to match the treatment to the individual. In the past several years, researchers have realized just how much the impacts of stress



An adhesive sensor can give quantitative readouts of several biological markers of stress.

vary depending on someone's biology, past exposures and present circumstances.

For one thing, men and women tend to differ in their responses⁶. Men show greater cortisol responses to stressors related to performance, for example, such as public speaking, whereas women might react more strongly to interpersonal stressors⁷. Some studies find that people whose microbiome is out of balance, because of antibiotics or previous stressors, can experience an exaggerated stress response.

There's also a body of research on how children who experience abuse or chronic neglect can be predisposed to a maladaptive stress response later in life. "An early-life traumatic experience can lead you to believe the world is unpredictable and unsafe place," says Slavich.

In the future, Slavich says, having a comprehensive profile of a person could guide a health-care team to the best combination of interventions for them.

He and his team are testing such an approach by pairing personal stress profiling with tailored treatments. The team matched more than 400 participants in California to one of five 12-week interventions on the basis of how individuals reported being affected by stress⁸. The treatment programmes focused on improving either sleep, eating habits, physical activity, cognitive responses or social relationships through weekly pre-recorded videos, digital modules, a coaching session and an assessment. The researchers are now analysing data collected on a variety of psychological, emotional, biological and behavioural outcomes – from sleep to the diversity of bacteria in the gut.

Rewiring resilience

Other treatment options could emerge from new ideas about how stress contributes to disease in the long-term. One theory centres on mitochondria, the powerhouses of cells.

It suggests that psychological stress drives disease and accelerates ageing, in part, by using up too much cellular energy⁹, creating oxidative stress that can damage cells and tissues. And because mitochondria are extremely sensitive to inflammation and oxidative stress, the effects can amplify in a harmful feedback loop.

Martin Picard, a psychobiologist at Columbia University in New York City and one of the proponents of the link between mitochondria and ageing, says it could explain many of the ways in which stress affects the body – including greying hairs. During a bout of grant-writing stress in 2017, five of his own auburn hairs turned grey, reverting back after a holiday.

"Hair colour is one of the most futile, dispensable features of our bodies," says Picard. "If the body runs out of energy, it makes sense that it would 'de-prioritize' making pigment for hairs."

Picard suspects that interventions, including meditation and exercise, could help to boost the quality and function of mitochondria. And if the theory is correct, it might even support the use of psychedelic therapy for people with post-traumatic stress and other stress disorders, he says. There are early hints that psilocybin, LSD and other hallucinogens act on a cell-surface receptor¹⁰ that seems to be involved in increasing the production of healthy mitochondria.

Targeting the microbiome is another emerging avenue. Research over the past couple of decades points to bidirectional communication between the brain and gut, with stress disrupting the microbiome and a disrupted microbiome exacerbating the stress response.

John Cryan, a neuroscientist at University College Cork in Ireland, and his team have shown that supplementing the diet with specific strains of gut bacteria that are naturally present – yet often depleted – dampened the stress response in both laboratory animals and humans. The same effects didn't show up in

mice with a severed vagus nerve¹¹, pointing to that nerve's central role in gut–brain communication, says Cryan. Research by Mendes and others is also showing that direct stimulation of the vagus nerve might modulate the stress response.

Finding solutions doesn't just benefit the individual. Through behaviours driven by stress and inflammation – including impaired decision-making – one person's stress can make others stressed, says Julia Concetta Arciero, a mathematician at the University of Indiana in Indianapolis.

Last year, Arciero co-authored a paper that used mathematical models to study the links between individual stressors and large-scale societal dysfunction over time¹². "The decisions people make, the actions they take, they're all very interactive without us realizing it," says Arciero.

Almeida, who wrote an editorial¹³ accompanying the paper, says the effects of stress go beyond individuals and beyond health problems. "If we're not making good decisions, or we can't help each other because we're all stressed, that could be a daunting future."

But eliminating stress entirely is not the answer, says Elissa Epel, a behavioural scientist at the University of California, San Francisco, and a pioneer in research on the mitochondria–ageing theory. Even though stress often causes damage at the cellular level, research by her team and others shows that brief bouts of well-regulated stress can bolster mental and physical health and strengthen resilience to future stress¹⁴.

Stress can even fuel action and ignite a positive feedback loop that might mitigate the burden of stress across society, says Almeida. Whether the stress is driven by moral outrage at injustice or by climate change, "it's motivation for activism", he says. "That typically doesn't happen if you don't feel threatened or challenged."

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