Targeting the mind/body connection in stress

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Our ability to cope with stress depends on how efficiently our body and mind regulate their response to it. Poor recovery from extremely stressful encounters can trigger post-traumatic stress disorder (PTSD), depression, or even chronic somatic dysfunction (such as pain and fatigue) in some people. Insight into the multi-level sequence of events—from cellular changes to brain function, emotional responses, and observed behavior—will help medical professionals make more informed decisions concerning interventions.

A new Tel Aviv University study published in *PLOS ONE* provides it. Researchers have used cutting-edge genetic research and brain imaging technologies to determine that the brain function responsible for regulating our stress response intertwines with molecular regulatory elements to produce a personal profile of resilience to stress. Their findings may lead to a future blood test that would facilitate preventive or early intervention in professions prone to high stress or trauma (combat soldiers and policemen, for example).

The research was led jointly by Prof. Talma Hendler of TAU's Sagol School of Neuroscience and the Director of the Functional Brain Center at Tel Aviv Sourasky Medical Center and Dr. Noam Shomron of TAU's Sagol School of Neuroscience and Sackler School of Medicine. Research for the study was conducted by TAU doctoral students Dr. Sharon Vaisvaser and Dr. Shira Modai.

The biological complexity of stress

"We can't look at one measurement at one point in time and think we have the whole picture of the stress response," Prof. Hendler explained. "This is perhaps the first study to induce stress in the lab and look at resulting changes to three levels of the stress response—neural (seen in brain imaging), cellular (measured through epigenetics), and experience (assessed through behavioral report)."

"We found that vulnerability to stress is not only related to a predisposition due to a certain gene," said Dr. Shomron. "The relevant gene can be expressed or not expressed according to a person's experience, environment, and many other context-related factors.

"This type of interaction between the environment and our genome has been conceptualized lately as the 'epigenetic process.' It has become clear that these processes are of an utmost importance to our health and well being, and are probably, in some cases, above and beyond our predispositions."

The research for this study was conducted on 49 healthy young male adults. Researchers integrated the analysis of fMRI images of brain function during an acute social stress task and also measured levels of microRNAs—small RNAs that exert potent regulatory effects—obtained in a blood test before and three hours after the induced stress. Dr. Vaisvaser explains, "Twenty minutes after the stress drill ended, we had two groups: the sustainers, those still stressed, and the recovered, those no longer stressed. The sustainers either didn't go back to baseline or took much longer to do so."

The researchers found that a specific alteration in the expression of the microRNA miR-29c was greater among the stress sustainers, implying a marker of slow recovery. Intriguingly, this change corresponded with modified connectivity of a major stress regulation node in the brain, the vento-medial prefrontal cortex (vmPFC).

The researchers were able to interpret functions in the brain through RNA molecules tested in the blood. They found that miR-29c played a mediating role, linking the enhancement of vmPFC connectivity with the anterior insula, a core node in the saliency network, sustaining the feeling of stress.

From basic research to practical treatment

"We all need to react to stress; it's healthy to react to something considered a challenge or a threat," said Prof. Hendler. "The problem is when you don't recover in a day, or a week, or more. This indicates your brain and'or body do not regulate properly and have a hard time returning to homeostasis (i.e., a balanced baseline). We found that this recovery involves both neural and epigenetic/cellular mechanisms, together contributing to our subjective experience of the stress.

"Knowing the brain metric that corresponds to such genetic vulnerability will make it possible to develop a personalized plan for brain-guided treatment based on a blood test."

"If you can identify through a simple blood test those likely to develop maladaptive responses to stress, you can offer a helpful prevention or early intervention," Dr. Shomron added.

"Conducting a collaborative interdisciplinary study is a great challenge," said Dr. Vaisvaser. "But the challenge is worth it, opening up new ways of looking at dynamics between concurrent factors contributing to the overall experience of stress."

The researchers are currently taking the study forward to look for the dynamic oscillations in the epigenetic markers of people suffering from stress disorders to confirm whether they can be modified via brain-targeted treatments.

Provided by Tel Aviv University

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