Stress, Inflammation, and Suboptimal Treatment Outcomes: Research Points to a New Paradigm

Psychoneuroimmunology explores links between stress, inflammation, and health

Materials and manuscript prepared by Andrew Stokesbury, Dr Emily Wyckoff, and Victoria Peluso

Stress often leads to changes in sleep patterns, diet, and overall well-being. Recent research has shown that stress can also cause inflammation, which in turn is a causal factor and enabler of worse outcomes in many chronic medical conditions.

These new insights have been studied in the field of psychoneuroimmunology (PNI), which has examined associations between immunity, inflammation, the endocrine system, and the central and peripheral nervous systems.

The Magnolia Innovation team, in an effort to better understand this emerging body of research, sat down with Dr George Slavich, a leading health psychologist primarily interested in the biomechanics and assessment of stress. Dr Slavich's research on the impacts of stress illuminates the importance of considering the psychoneuroimmunology perspective in domains such as clinical trial design, patient assessment and diagnosis, and monitoring treatment effectiveness.

In this interview, Dr Slavich and Magnolia Innovation team member Dr Emily Wyckoff discuss the data underlying psychoneuroimmunology and how it points to the need to assess stress and better integrate those assessments into treatment plans to achieve optimal care outcomes.

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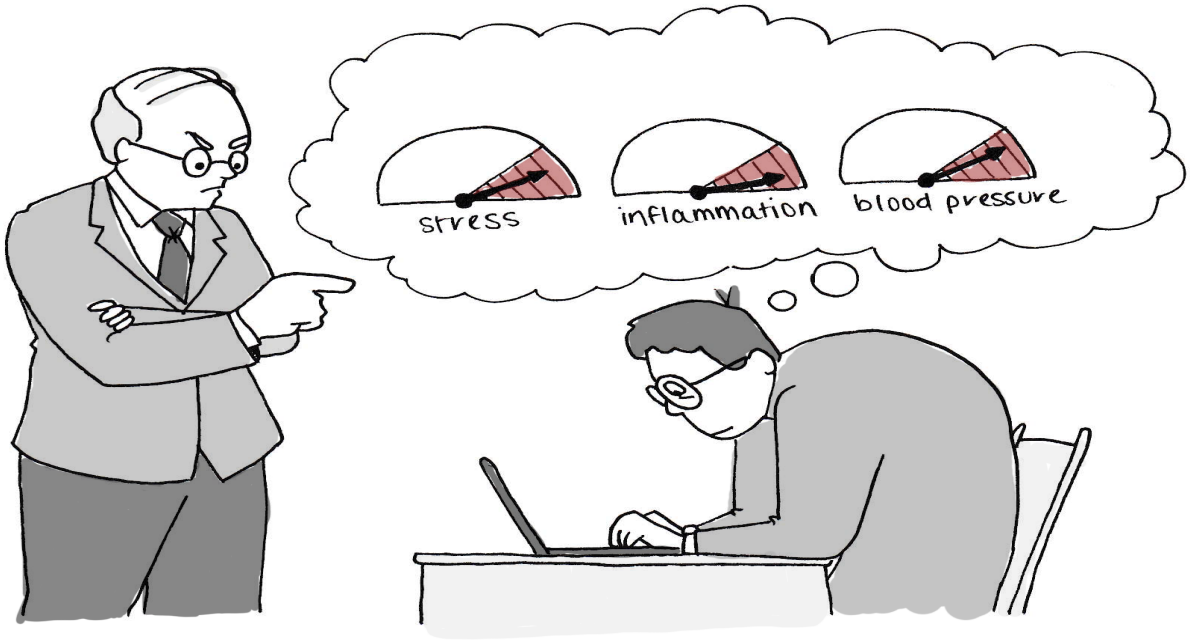


"...and another thing..."

Dr Wyckoff: Thank you for taking the time to talk with us, Dr Slavich. To get started, can you please define psychoneuroimmunology?

Dr Slavich: In some ways, it is really complicated, and in other ways, it's pretty simple. The simple part is just to break that word down into its three components: psychology, neuroscience, and immunology. A great example is you have an exam or have an argument with a boss. You are in that stressful situation; you have thoughts that pop into your head like, "This isn't going well. It's never going to end." Those thoughts (psychology) influence the activity of the brain (neuroscience), and the activity of the brain influences the immune system (immunology). And there you go, now you have psychoneuroimmunology, or PNI.

Dr Wyckoff: How would you explain PNI to a medical professional?

Dr Slavich: Oncologists have known for a while that inflammation can increase risk for the development of tumors. Cardiologists know that inflammation is involved in heart disease. Building on this, in 2010, *Science* magazine came out with an issue looking at the top 10 most important discoveries of the previous decade. One was the involvement of the immune system and inflammation in chronic disease risk. What the *Science* article noted is that inflammation has now hit the big time in the sense that it is now viewed as a common risk factor, linking psychosocial experiences with disease risk in general. One very important nugget in there, which hasn't been fully appreciated until more recently, is that…

> **"…experiences of stress don't just lead to negative thoughts and emotions; they also greatly impact the immune system."**

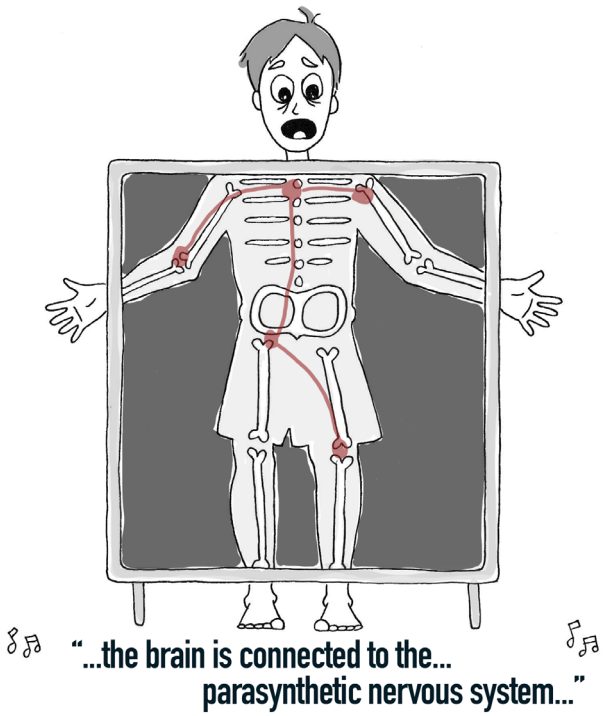
When inflammation increases over a short period of time, it can lead to accelerated wound healing and recovery; it can limit the spread of infections and things of that sort. But if you are stressed out for a long period of time, one of the consequences is that you are also increasing inflammation for a

long period of time. If that inflammation becomes chronic, then it can damage cells and organs in the body and lead to things like increased risk of cancer, heart disease, and depression. So, medically speaking, PNI attempts to understand how these associations lead to morbidity and mortality in these contexts.

Dr Wyckoff: Why do you think medical communities have not really engaged with this idea of stress's role in inflammation?

Dr Slavich: In a lot of medical textbooks, the brain and the peripheral immune system are described as separate systems that do not interact. The idea that the brain regulates the immune system or that the peripheral immune system can have an influence on the brain is not written into most medical textbooks.

In 2015, though, a postdoc at the University of Virginia was looking through a microscope and saw very small blood vessels running down the brain stem of rodents. He realized that this was a physical structure in the body that allowed factors circulating in the brain, like immune cells that were being released or trafficked around the brain, to actually move to the periphery. If you are saying that something happening in the brain is affecting the rest of the body, then you have to be able to say how that's occurring.

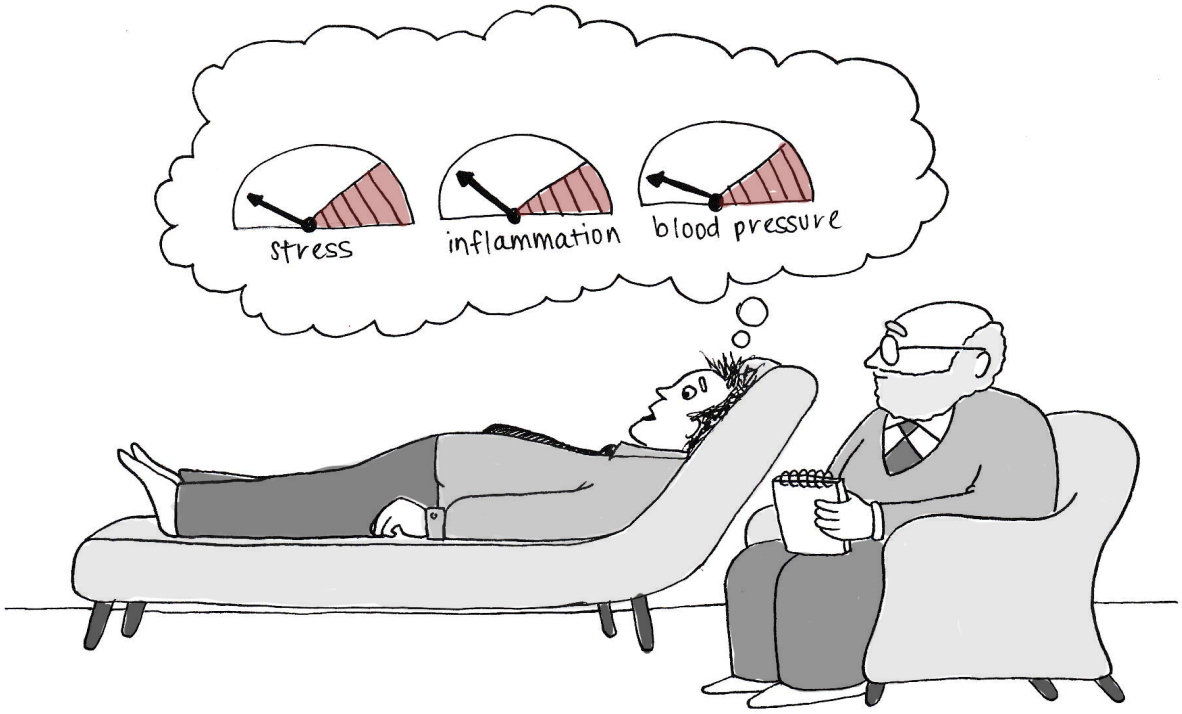


So, it is a very long-winded way of saying that those mechanistic pathways were not known until 2015, which is why the medical model does not include a description of the pathways that link mind, body, and medicine. But now we know what they are and now those training programs should be updated and revised to reflect the fact that the brain and the body are physically connected. I think that needs to be better appreciated in the practice of medicine.

Dr Wyckoff: You also make a connection between stress, inflammation, and depression.

Dr Slavich: Our research has shown that a key process linking stress and depression for many people is inflammation. Sickness behaviors include things like social and behavioral withdrawal, malaise, fatigue, et cetera, and these sickness behaviors are driven by inflammation and other related immune processes that can be activated by stress. And what is interesting is that a lot of these sickness behaviors map on very closely to depressive symptoms.

Take chronic pain in the context of depression, for example. Somewhere around 75% to 85% of individuals with chronic depression also report pain symptoms. Cytokines, which drive the inflammatory response, can also lead to increased pain sensitivity. So, in that case, the root of both depressive symptoms and chronic pain symptoms lies in their common biology, which is inflammation. A lot of other disorders also involve inflammation. One way to think about it is that chronic stress leads to systemic chronic inflammation, which over a long period of time, is going to increase the risk for all of these physical or somatic disease conditions that have an inflammatory component.



"...I'm feeling a lot better now."

Dr Wyckoff: Can you speak a little more to where psychoneuroimmunology fits within the biomedical versus psychosocial model?

Dr Slavich: Our research has shown that there are several evidence-based psychosocial interventions that can help reduce inflammation. If you are a psychologist working with a stressed patient, you might focus on reducing interpersonal conflict in the person's life, or having them view the world in a more balanced, positive, optimistic light. You could imagine inoculating your patient from having a stress response by reminding them of their capacities, or that they've practiced this before and that they're ready to go. The point is to prepare them for the stressor and also to get them to view the situation as a challenge as opposed to a social threat. But that is just the psychology of it. There are so many other cool ways to intervene that greatly impact the immune system. There are anti-inflammatory diets. Sleep is one of the biggest drivers of inflammation. So, if you have a poor night of sleep, you are going to wake up inflamed. If you have a job that leads you to have poor sleep five days a week, then you are going to be chronically inflamed. In addition, exercise is a factor that not only leads to your sympathetic nervous system being more tightly controlled but can also make you leaner. And over time, all of these things can reduce your risk for chronic inflammation and negative inflammation-related health outcomes.

Dr Wyckoff: Can you speak a little bit to what pharmacological interventions might typically be of use?

Dr Slavich: There's a lot of talk about pharmacological interventions that could be useful. What I want people to understand is that targeting stress is also a critical health-relevant intervention. Take people coming into a clinic who have chronic autoimmune problems or chronic somatic symptoms that have gone unresolved, for example. They might be stressed out, but stress is almost never formally

assessed in these contexts. So, for asthma, a provider might prescribe a localized anti-inflammatory, but in my experience, the stress that the person is experiencing—which is likely contributing to their symptom exacerbation—is never assessed or addressed. So, one source of the problem—the stress that people are under—is not removed.

> **"To put it simply, stress is one of those things that's on everybody's minds but in nobody's charts, and if it's not assessed, then it can't be addressed."**

That is the issue. If you do not assess the stressors that people are experiencing, then it is not even considered as a risk factor that is in turn dealt with clinically.

> **"We need to be assessing stress levels in the clinic to reduce disease risk and improve peoples' lives."**

Dr Wyckoff: So, presuming that the medical community embraces PNI, how does that change the delivery of care?

Dr Slavich: I guess in the lingo, this might be called practicing functional medicine, holistic medicine, or integrative medicine. These are terms providers use when they are able to spend more than 15 minutes with a patient and actually do a comprehensive assessment. You are not just asking about symptoms, you are also asking about lifestyle, stress levels, and sleep. You are doing a comprehensive assessment of these different risk factors or processes that could be leading to the clinical presentation. So, what does PNI-informed healthcare look like? Well, it should certainly include assessing people's stress levels, diet, sleep, physical activity, social relationships, and more to understand the roots of disease risk.

"...check...check...check..."

Dr Wyckoff: What care providers are best situated to do this sort of comprehensive assessment?

Dr Slavich:

> **"If we start talking about the PNI model only being relevant for mental health, then I think we've actually missed the big picture…"**

…which is that many chronic diseases are not mental health problems. Rather, they are asthma, rheumatoid arthritis, chronic pain, heart disease, cancer, and cognitive decline. So, these are the types of health problems that likely stand to benefit most from conducting stress assessments, simply because stress is rarely formally assessed in these contexts.

In California, if you are licensed to provide medical services, then you can now be reimbursed for doing a stress assessment. That's a huge step forward, but it's only a start because California is only one state. Ultimately, primary care providers need to be reimbursed for more comprehensively

assessing patients so that they can make time available to do these assessments—not just of stress but of social relationships, diet, sleep, and exercise. It has to be on the radar of the primary care provider.

Dr Wyckoff: On the subject of mental health, can you speak to how PNI may relate specifically to mental health treatment?

Dr Slavich: Part of that is an easy answer, which is that we do not have an experimental medicine approach to mental health treatments. I think this has started to change, but very slowly. The experimental therapeutics approach involves running clinical trials, learning what works as quickly as possible, and then innovating, testing, innovating, and testing, and then once you've hit the benchmarks you want for effectiveness and efficacy, you roll it out. People would benefit from the innovation of that sort of experimental medicine. But this experimental therapeutics approach is not the current model in mental health.

Dr Wyckoff: Thinking about how this affects clinical trials, if we are not taking stress and inflammation into account, are we missing out on correcting a key confounding variable?

Dr Slavich: There are health behaviors that are oftentimes at the top of researchers' minds—things like smoking, diet, and physical activity. But even in population-based representative samples of the United States, we do not have great measures of stress. So, yes, if a randomized clinical trial is focused on a chronic disease condition, I would argue that it needs to assess both stress and inflammation to understand how these factors may be contributing to the chronic disease being studied.

Dr Wyckoff: Is there a disease space that you think does particularly well with the experimental medicine model?

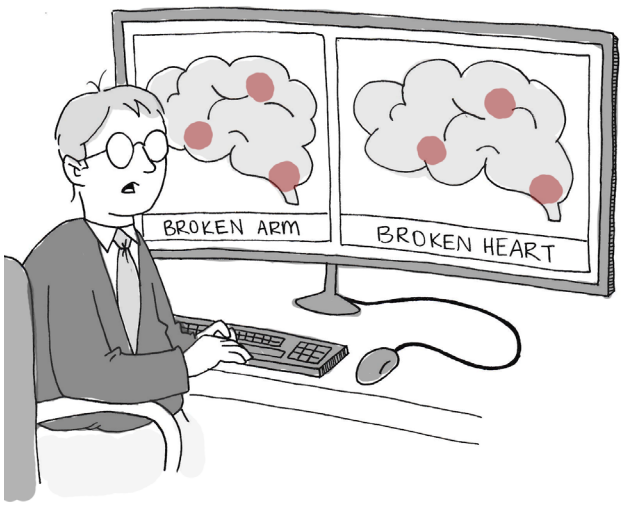
Dr Slavich: In general, cancer treatments, especially terminal cancers, where it is literally a life-and-death situation and the health burden is astronomically high. People are willing to take a greater risk for the payoff of living longer. But I think also because cancer genomics have a history of trying to identify, in a very precise way, the genotype and the phenotype of the problem and then trying to map on the treatments to the genotype and the phenotype. Precision medicine grew in large part out of this very specific approach, and I think there's a lot we can learn from that.

Dr Wyckoff: What are the top couple of things that you would like the pharma industry to be aware of when you think about the future of PNI in medicine?

Dr Slavich: I think it's critical for folks to understand stress biology from a systems perspective. We've studied and documented the core stress pathways: the sympathetic nervous system, HPA axis, immune system, and vagus nerve. If more people had a high-level understanding of those four mechanistic pathways and how they are activated by stress, then different strategies would immediately come to mind for short-circuiting these pathways and reducing individuals' risk for stress-related health problems.

Dr Wyckoff: We're seeing more use of serotonin–norepinephrine reuptake inhibitors to help people with chronic pain. Are there other examples of awareness of this mind/body connection in specific disease areas?

Dr Slavich: Some of the most interesting work we have done is on the neurobiological overlap of physical pain and social pain. If you put somebody in fMRI scanner and you put a heat pad on their leg to induce physical pain, or if you put somebody in an fMRI scanner and you socially reject them and induce social pain, you see some of the same neural substrates activated. That is really fascinating to me because a lot of people who



"Wow, physical pain and emotional pain are the same!"

feel rejected in their daily life also experience physical pain. It is a bidirectional pathway, whereby experiences of social stress can contribute to physical pain and, potentially, vice versa.

Looking at the neurobiology of pain, we know there is an oxytocin-release component of the pain experience. Sometimes, those intervention strategies are thought of in terms of reducing physical or social pain symptoms, but often not. To examine how an intervention that is typically used to reduce physical pain might affect peoples' perceptions of social pain, we did a small randomized clinical trial where we administered acetaminophen for three weeks and showed that it reduced peoples' daily levels of social pain. So, what we thought is, if that is true, then you should be able to target the physical pain pathway and, in doing so, reduce experiences of social pain. I think the ability to reduce pain signaling in the brain is interesting and somewhat novel. We do not yet have a lot of great anti-inflammatory strategies that have benefits without causing other problems. But that is something we can get better at.

Psychopharmacology is not my training, but what I can say is that we need greater innovation on anti-inflammatories that have more benefits and fewer costs. These anti-inflammatory strategies may not just have benefits for somatic symptoms but may also benefit things like anxiety disorders, depression, PTSD, and perhaps many other conditions that have an inflammatory component.

Magnolia Innovation is a pharmaceutical market research firm that believes in following the science where the evidence leads and is unafraid of new and unorthodox ideas. We are grateful to Dr Slavich for sharing his research and observations on the links between stress, inflammation, and chronic disease.

For more information on these and many other new developments on the frontiers of healthcare, pharmacology, and related areas, please contact Magnolia Innovation, or visit magnoliainnovation.com.

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