Received: 7 June 2024 | Revised: 7 June 2024 | Accepted: 8 June 2024

DOI: 10.1002/jts.23083

COMMENTARY

What I was thinking/what I would do differently: Biological markers and mechanisms of mental health

Raül Andero[1,2,3,4] | **Tanja Jovanovic**[5] | **Murray B. Stein**[6,7] | **Arieh Y. Shalev**[8]

[1]Centro de Investigación Biomédica En Red en Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

[2]Unitat de Neurociència Traslacional, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT), Institut de Neurociències, Universitat Autònoma de Barcelona, Bellaterra, Spain

[3]Departament de Psicobiologia i de Metodologia de les Ciències de la Salut, Institut de Neurociències, Universitat Autònoma de Barcelona, Barcelona, Spain

[4]Catalan Institute for Research and Advances Studies (ICREA), Barcelona, Spain

[5]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, Michigan, USA

[6]Department of Psychiatry and School of Public Health, University of California–San Diego, La Jolla, California, USA

[7]VA San Diego Healthcare System, San Diego, California, USA

[8]Department of Psychiatry, New York University Grossman School of Medicine, New York, New York, USA

Correspondence
Raul Andero, Office M1-141, UAB Campus. Cerdanyola del Vallès, 08193. Barcelona, Spain. Institute of Neuroscience, Autonomous University of Barcelona, ICREA.
Email: raul.andero@uab.cat

Funding information
La Caixa, Grant/Award Number: HR22-00737; United States Department of Veterans Affairs, Grant/Award Number: I01CX001849; Red Española de Investigación en Estrés/Spanish Network for Stress Research RED2022-134191-T, Grant/Award Number: MCIN/AEI/10.13039/501100011033; ERANET-Neuron, Grant/Award Number: JTC 2019 ISCIII AC19/00077; National Institute of Mental Health, Grant/Award Numbers: R01 MH129495, R01MH106595, R21 MH092576, U01 MH087981; United States Department of Defense through Henry Jackson Foundation, Grant/Award Number: HU0001-15-2-0004; RETOS-MINECO, Grant/Award Number: PID2020-112705RB-I00; Fundación Koplowitz

Abstract

At the 39th meeting of the International Society of Traumatic Stress Studies, four leading scientists and clinicians were invited to reflect on their careers, focusing on the biological mechanisms and markers of traumatic stress. Dr. Raul Andero has contributed to understanding how stress alters memory networks in the brain, influencing the development of novel treatments. Dr. Tanja Jovanovic has pioneered the measurement and mechanistic understanding of fear learning, bridging basic and clinical research. Dr. Murray B. Stein has scaled up clinical and lab observations to large populations, refining the field's understanding of traumatic stress. Dr. Arieh Y Shalev has shaped the definition of traumatic stress, pioneering the longitudinal investigation of stress and integrating advanced computational methods to identify individuals at risk. These panelists were asked to reflect on their initial problems, ambitions, concerns, and unexpected challenges, as well as the influence of their work, on new research trajectories. Their insights provide valuable lessons about the process and content of their work, and their pioneering efforts have significantly advanced our understanding of the biological mechanisms and markers of traumatic stress.

Four leading scientists and clinicians were invited to the 39th meeting of the International Society of Traumatic Stress Studies to answer a simple question: "What was I thinking?" The unifying theme for this otherwise diverse panel is that all these individuals have made biological mechanisms and markers of traumatic stress a focal point of their careers.

Raul Andero, PhD, is a Catalan Institution for Research and Advances Studies (ICREA) Research Professor at the Institute of Neurosciences and the Department of Psychobiology and Methodology of Health Sciences at the Autonomous University of Barcelona in Spain. His research has focused on understanding how stress changes memory networks in the brains of both rodents and humans. Dr. Andero's work has uncovered novel mechanisms of pathology and resilience that have had a profound influence on the pipeline that begins at basic science and moves toward more specific and timelier novel treatments.

Tanja Jovanovic, PhD is a professor of psychiatry and the David and Patricia Barron Chair in PTSD Neurobiology in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University (Detroit, Michigan, United States). Dr. Jovanovic has both pioneered and scaled the measurement and mechanistic understanding of fear learning. Her research paradigms are ubiquitous in both basic and clinical research, having built a bridge that has allowed for the discovery and dissection of numerous biological mechanisms of traumatic stress and resilience.

Murray B. Stein, MD, MPH, FRCPC, is a distinguished professor of psychiatry and public health at the University of California San Diego (La Jolla, California, United States) and a staff psychiatrist at the VA San Diego Healthcare System. Dr. Stein is one of the clinician–scientists who have helped define the field's understanding of traumatic stress. Across his career, he has scaled up what has been observed in the clinic and lab for study in large populations, allowing the field to progressively move to observational methods of diagnosis and treatment at a world population level.

Arieh Y. Shalev is a professor emeritus of psychiatry at the Hebrew University School of Medicine's Hadassah Medical Center in Jerusalem, Israel and an adjunct professor of psychiatry at NYU Grossman School of Medicine in New York. Dr. Shalev likely encapsulates the most holistic perspective on traumatic stress at present. His early work following his experiences as a military psychiatrist deployed to war helped shape the very definition of traumatic stress. His early studies at Hadassah Hospital with his long-time collaborators Roger Pitman and Scott Orr were the first to map the basic biological mechanisms of stress and fear to the clinical course of traumatic stress. Dr. Shalev pioneered the longitudinal investigation of stress, which directly influenced the field's understanding of the time course of recovery and pathology. Owing to the diversity of mechanisms, pathways, and time courses of traumatic stress that Dr. Shalev identified, he further pioneered the integration of advanced computational methods to identify individuals at risk.

These panelists were asked to answer the following questions as they reflected back on their long and diverse careers. Their answers are lightly edited for clarity.

1. What were the burning problems you were hoping to solve when you first started investigating this area?
2. What were your greatest ambitions when you first started? What were you hoping to accomplish?
3. What were you concerned with when you started down this path?
4. What were the unexpected problems and frustrating failures that encouraged rethinking?
5. How has your work influenced the trajectory of new lines of research you could not have envisioned when you first started?
6. What are important lessons you learned both about the process and content of your work?

What were the burning problems you were hoping to solve when you first started investigating this area?

Stein: I entered medical school not knowing what I was hoping to solve, but I knew I wanted to be involved in research. By serendipity—or you might call it fate—my psychiatry rotation as a medical student had me working on the consultation–liaison service. On the service, I could see how disorders of the mind, brain, psyche, and body were interrelated, and how someone could work in psychiatry and still be embedded in medicine. When I entered psychiatry as a resident, I was once again granted some excellent luck: A psychologist on the inpatient unit where I was working was conducting a clinical trial among patients with agoraphobia, which gave me the opportunity to meet with many individuals whose anxiety and avoidance symptoms were significantly impairing their lives. I decided then that this was a group of individuals I wanted to work with, better understand, and help reempower to take control of their lives. I don't think I had grand ideas at the time about how to make that happen, but that experience pointed me in the direction of seeking additional training in anxiety-related, and later trauma and stressor–related, disorders.

Jovanovic: I was always very passionate about understanding how nature and nurture interact to form behavior. In my dissertation, I conducted a cross-fostering study in monkeys in a model of maternal abuse; I wanted to know

whether such aberrant behavior was learned or inherited. When I was a postdoc at the Grady Trauma Project at Emory University School of Medicine in Atlanta, Georgia, I was investigating the Gene x Environment interactions (G x E) in posttraumatic stress disorder (PTSD), which is essentially nature and nurture. I also wanted to understand the origins of risk and resilience during child development, adding the "D" in the G x E x D interaction. I was hoping that having a good understanding of these mechanisms would provide a roadmap to be able to detect early signs of dysfunction and prevent the onset of illness.

Shalev: A year after starting my residency in psychiatry, I was enlisted as a medical officer in Israel's 1973 Yom Kippur War. We knew very little about stress disorders, blindly followed the two World Wars' frontline psychiatry principles, and creatively provided in-line and postwar care for the bereaved and maimed. The burning problems were both practical and conceptual: I was surprised to see that some of my patients fairly survived trauma, whereas others' lives were devastated. I took notes, tried to make sense of what I saw, and tried to help. Document, understand, and help remained my burning questions in the following decades. With the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*; American Psychiatric Association, 1980) 7 years later, the idea of PTSD shifted the focus of my work to evaluating the viability of the newly formulated disorder by generating layers (e.g., descriptive, physiological, neuroendocrine) of factual knowledge.

Andero: I studied psychology and always wanted to find new successful therapeutic approaches to prevent and treat fear-based disorders. To achieve this goal, I always thought it was key to increase awareness of the combination of experiments in animal models and humans because interspecies studies allow highly valuable questions and answers in neuroscience. My practical experience started with an internship as a clinical psychologist. This was a wake-up call on how urgent it is to find help for so many people suffering from mental health concerns. After this experience, I started working with animal models, adding molecular biology studies during my PhD (Andero et al., 2011) and later combining them with human experiments during my postdoctoral period at the laboratory of Kerry Ressler and later at my laboratory (Andero et al., 2013; Velasco et al., 2022; Florido et al. 2024).

What were your greatest ambitions when you first started? What were you hoping to accomplish?

Shalev: My path to PTSD research was shaped by three converging forces: being a clinician, the repeated occurrence of wars and terror throughout my career, and an ever-present dissatisfaction with canonical knowledge. Working in Israel's largest receiving hospital, I was able to evaluate and treat trauma survivors upon emergency department (ED) admission and follow them, often for years. This shaped my still-unfulfilled ambition: To crack the code of PTSD etiology and pathogenesis. The resulting longitudinal research comprised descriptive psychopathology, psychophysiology, endocrinology, brain imaging, gene expression, prediction, prevention, and treatment. I was blessed by friendships with eminent content experts (e.g., Roger Pitman, Scott Orr, Rachel Yehuda, Talma Hendler, Daniel and Lynda King), who helped me explore pertinent facets of the same quest and guarded me from slipping, method- or content-wise.

Jovanovic: As someone who studies the brain, I believe that mental illness stems from neurobiological alterations. I would say my greatest ambition would be that we could cure most illnesses by directly observing and changing brain dysfunction. Ideally, treatments would target this dysfunction rather than *DSM*-defined disorders. When the National Institute of Mental Health (NIMH) proposed the Research Domain Criteria (RDoC) framework (Insel et al., 2010) in which neurobiological mechanisms would be the focus of mental disorder research, I was very excited and hoped this would move the field forward toward this ambition.

Andero: My greatest ambition was, and still is, to translate findings from experiments in animal models to the clinic, focusing on biological biomarkers. I quickly learned that it is especially important during the initial years of one's career to learn as many different techniques and approaches as possible to have a wide view of the field. Specifically, 20 years ago, the field was very ambitious, and it was generally believed that by 2024, it would likely be more advanced in the treatment of fear-based disorders than it currently is. Researchers are learning from failed clinical trials and the lack of translatability of some animal models, focusing now on more holistic approaches that are likely to be more successful.

Stein: When I started out, my greatest ambition was to develop new treatments for anxious and avoidant patients. I was struck by how patients with these disorders were, for the most part, logical and insightful about their mental health problems. The agoraphobic patients, for example, could tell me that it was ridiculous for them to be paralyzed by their fears, yet they couldn't overcome them. I was fortunate, early on in my psychiatry training, to be exposed, so to speak, to the magic of behavioral therapies. My greatest ambition at that time was to eventually understand enough about how these disorders were instantiated in individuals, how exposure-based therapies worked to combat these problems, and how they might be combined with new

medications that were being developed to provide relief or maybe even a "cure" for those suffering from these problems. This grand ambition was, and still is, a good target to aim for. I've learned over the years that progress along these lines can be painstakingly slow—I've been working in this field for nearly 40 years, and I can't say that this goal has been achieved, but I do believe that the field is getting there. I step back from time to time and marvel at what my colleagues have achieved when it comes to treating anxiety and trauma and stress–related disorders. Progress has, without a doubt, been made, and it continues to be made with the entry of talented young clinician-scientists with their own grand ambitions and new expertise and tools to address these challenging goals.

What were you concerned with when you started down this path?

Andero: I have always been concerned about how improvements in mental health are not equally available to all individuals. I believe in equal opportunities in treatments for mental health for everyone. This can be achieved through a strong system of universal health care.

Stein: I don't think I was smart enough to have concerns. At the graduation ceremony from medical school, one of the senior, very respected medical researchers came up to me and asked what area of medicine I would be continuing in. When I told him I was going into psychiatry, he looked appalled—well, maybe "saddened" is a better description. He said, "Psychiatry is far too complicated, not enough is known about the brain, and it's going to be very difficult to do research." I nodded and thanked him for his advice, but I remember thinking, "Those are exactly the reasons to go into psychiatry and to start a research career in mental health. There is so little known, anything I am able to contribute can have a positive impact."

Shalev: I don't think that researchers of my generation had major concerns when they started their paths. The questions were clear, unexplored, and original; the case material abundant; and the field eagerly accepted and advanced those with enough energy to pursue trauma research. Concerns came later, however, with the dilution of the PTSD construct; the ever-changing diagnostic templates; the yet-unresolved translations of animal research to human trauma; and the increasing emphasis—and funding for—evaluating remote causal or risk factors, such as genetic architectures, in a landscape increasingly flattened by the wider inclusion of ever-larger and, therefore, heterogeneous samples. My other major concern is the lack of a binding theory of trauma-triggered conditions and the quasi-elimination of interpersonal, social, and spiritual determinants of stress disorders' initiation and trajectories.

Jovanovic: I was concerned that the tools to study the brain in humans were limited. Though neuroimaging methods have improved over the years, and we have better resolution to observe changes in the brain, we still cannot "see" circuits with enough detail to determine whether someone is mentally ill. Therefore, we still rely heavily on patient self-report of symptoms and do not have objective biological measures (or biomarkers) of mental disease. Often, the gold-standard assessments are influenced by subjective or retrospective bias, and so we don't have a "ground truth" for comparisons with neurobiology. When self-report and biological assessments don't match—for example, if someone says they are not distressed but show exaggerated fear responses—which is the more accurate basis for treatment?

What were unexpected problems and frustrating failures that encouraged rethinking?

Jovanovic: A significant barrier to understanding the causes of mental illness in humans is the inability to truly manipulate brain mechanisms—animal research can be very helpful in determining how and why neurobiology works. In a series of translational experiments, we found that deficits in fear extinction seen in humans with PTSD could be attenuated by suppressing the stress hormone cortisol using dexamethasone (Jovanovic et al., 2011; Michopoulos et al., 2017). The same drug-facilitated fear extinction in a mouse model (Sawamura, 2016), so we tested it clinically by pairing the drug with exposure therapy in PTSD patients; however, the clinical trial failed, as most patients dropped out of the study after taking dexamethasone (Maples-Keller et al., 2019). We realized that direct translation may not always apply in the real world outside the laboratory.

Andero: Nowadays, obtaining and managing funding is time-consuming, and it certainly takes time that could be focused on experiments and writing papers. So, my main rethinking has been generally due to failures and successes in obtaining funding that fundamentally shaped my lab's work. "Failed experiments" often come from leaning too much on an expected ideal result, which is rarely achieved due to the complexity of the issues in which we work. Instead, I think that usually, the best experiments are the ones in which the direction of the results does not matter because the experiment is successful in producing useful results, such as discovering biomarkers of fear-based disorders.

Stein: Doing research with human beings is fraught with challenges. Research participants drop out of clinical trials; they experience side effects that overwhelm

potentially therapeutic aspects of treatment; and their biology often doesn't translate, as Tanja mentions, in the way we imagined it would. But all those difficulties are to be expected when working with complex entities such as human beings, and the challenges of conducting clinical research keep me invested and excited in this field.

In terms of frustrations Raul's comments resonate with me. I've never enjoyed the exercise of grant writing and, having spent more than half my life writing grants—maybe in real-time—I sometimes think about the ideas that never got funded, the hypotheses that never got tested. I can't complain too much about the grant writing exercise because I've been fortunate enough to be federally funded for a long time. But I'd be lying if I said it was my best ideas that always got funded. They often didn't. I wish there was a better way to allocate grant funding than the current peer review process, but I don't have a solution in hand.

Shalev: Unexpected problems that encourage rethinking are the bread and butter of empirical research. When our pet PTSD predictor, auditory startle response (ASR), failed to predict PTSD and instead developed with PTSD (Shalev et al., 2000), or when the hippocampus (HC) did not shrink in PTSD, as the allostatic model predicted (Bonne et al., 2001), we learned something about the world: Smaller HC could be a vulnerability trait and abnormal ASR a PTSD-induced sensitization. Even when our initially hailed association between ED heart rate and chronic PTSD (Shalev et al., 1998) failed to be replicated, we humbly produced our own nonreplication in distressed terror survivors. ED's agitation and distress during mass terror evacuations were powerful enough to wipe out HR differences between survivors at risk and others, a difference that still existed among road traffic accident survivors. Such "frustrations" are fair game. All you need is a permissive ego and, sometimes, a friend—Isaac Galatzer-Levy—whose newly introduced latent growth mixture model revealed an ED low-cortisol signal in a subset of survivors with childhood trauma, turning negative results (Shalev et al., 2008) into positive ones (Galatzer-Levy et al., 2017).

How has your work influenced the trajectory of new lines of research you could not have envisioned when you first started?

Stein: I've never been someone who was wedded to a particular set of methods. I've always been focused on the clinical conditions, and I've tried to adapt the methods I use to the questions I want to ask at any given point in time. I've been fortunate, as new methods have come online, to be able to seek out and work with marvelous peers who have brought expert methods—and great ideas—to our collaborations. When I started out, PET imaging was available, though access was limited by site and cost, but functional magnetic resonance imaging (fMRI) was just kicking off. Once I could see that fMRI was going to provide new insights into psychopathology, I sought out collaborators with whom I could work to ask interesting questions. A decade later—or maybe it was two decades; time flies when you're having fun—when it became apparent that molecular genetics was going to unlock new information about the brain and mental disorders, I similarly sought out collaborators with whom I could work to leverage these new molecular analytical tools. I could not have envisioned, when I first started out, contributing to functional neuroimaging in anxiety disorders (Stein et al., 2002) or genomic studies in PTSD (Nievergelt et al., 2024; Stein et al., 2021) and other areas. But by working with the right people, and those I have worked with (you know who you are!) are not only technically savvy and incredibly smart but also wonderful, generous human beings, I have been able to stay current and, importantly, stay enthusiastic and excited about the work we do.

Shalev: The immediate responses to this question would concern a few first-of-kind studies that encouraged others to follow a line of inquiry. One that comes to mind is the Segman et al. (2005) peripheral blood mononuclear cells' gene expression association with PTSD, produced at a time when peripheral gene expression was thought to have nothing to do with the central nervous system's gene expression dynamics. Other such works include the ED heart rate study, the longitudinal MRI study, and some early persistent PTSD predictors. In retrospect, however, the innovation, and the new lines opened were a timing effect: As technologies developed, innovative studies became "the new normal." Locally, what brought my group to engage in early treatment studies was a lingering feeling, amidst a wave of terror, that while enrolling recent survivors in increasingly demanding studies, we did nothing to help them. For that shift, I am indebted to Sara Freedman, PhD, and other members of my group.

Jovanovic: When I started working in PTSD, the psychophysiological assessments involved relatively complicated experiments and expensive equipment. Though I still use these in my research, recent technological advancements using apps and mobile devices, such as tablets and smartphones, make it possible to measure physiological changes at a fraction of the cost and in almost any environment. These advancements are shifting the field to make it more possible to incorporate biological measures in a number of challenging settings, including emergency rooms (Hinrichs et al., 2019), clinicians' offices, fieldwork in developing countries, and home visits (Grasser et al., 2022). As digital phenotyping becomes more common,

physiological biomarkers can be added to provide objective assessments and aid clinical decisions.

Andero: I would not have expected that we work nowadays in such multidisciplinary teams. For example, in my laboratory, there are profiles such as psychologists, physicians, biotechnologists, and biologists. In neuroscience, technology has a significant the degree of importance nowadays (e.g., minimicroscopes that track neurons in real-time while the animal is behaving; Florido et al. 2024). Technology is less and less purchased, and teams create it themselves to maximize its customization. So, nowadays, the neuroscience field is dominated by neurotechnologists making systems neuroscience a predominant position.

What are important lessons you learned both about the process and content of your work?

Shalev: The first lessons that come to mind are: ask the big question, develop and borrow expertise in multiple domains, and remain clinically relevant. Following and equally important is this: For your findings to survive, make sure to map and express the particularities of your sampling and procedures. You are always in error, and it is most critical to map it and declare to which PTSD subpopulation your results are generalizable. To do that, keep a tab on those not included or unwilling to follow. We would not have been able to show that declining early treatment is harmful if we had not engaged individuals who declined in at least one follow-up call (Shalev et al., 2011). Similarly, we wouldn't know that 11% of participants who our enrollment interviewers defined as not needing treatment developed PTSD regardless.

Stein: That's a tough question to answer. I've learned so many important lessons, it is hard to home in on one or two. But if I go back to my experience as an early career clinician–scientist, I remember one of my mentors commenting on the fact that whereas I was collecting a lot of data, I needed to set aside time to write. He had a cartoon on the door of his lab that said, "Unlike wine, data does not improve with age." That message has stuck with me. I work hard to make sure I have time to think about the data we generate, and that I have time to write and get findings into press because that's how the information gets critiqued, often improved, and disseminated. And I try to convey the same message to those early career investigators I have the privilege to mentor.

Andero: An important and humbling experience I have acquired is that many of my most valuable scientific contributions have been due to serendipity. For example, in 2021, we published a study in which we discovered that the same drug could have opposite effects on memory functioning. Specifically, the neurokinin 3 receptor antagonist *osanetant* enhances memory in female mice whereas it impairs memory in males (Florido et al., 2021). We had been working with osanetant for several years in male mice, and we were not expecting this result the first time we dosed it in females. In the beginning, we could not believe the results, so we had to replicate the experiment to confirm this surprising and fascinating result.

Jovanovic: If I could go back in time, I would collect more data! Specifically, more information about genetics—saliva can be easily banked for future studies. Even if we could not anticipate what genomic or epigenomic information would be important to know, I believe that a small saliva sample will one day give us a wealth of biological information. I would also get information about when different events happened to individuals during development. While we know that childhood trauma has long-term consequences, there are particularly sensitive developmental windows, such as early childhood or adolescence. Prepubertal trauma can have very different effects on the brain and body than postpubertal trauma (Morrison et al., 2022); the information about when trauma happens is very important and is missed in most assessments of childhood trauma.

AUTHOR NOTE

This paper was edited by Isaac R. Galatzer-Levy and Katharina Schultebraucks.

Murray Stein was supported by the National Institute of Mental Health (NIMH; U01MH087981, R01MH106595), the U.S. Department of Defense (DoD) through the Henry Jackson Foundation (HU0001-15-2-0004), and the U.S. Department of Veterans Affairs (VA; I01CX001849). Tanja Jovanovic was supported by the National Institutes of Health (NIH; R21 MH092576, R01 MH129495). Raül Andero was supported by ERANET-Neuron JTC 2019 (ISCIII AC19/00077), Fundacion Koplowitz, a 2022 BBVA Foundation Leonardo Grant for Researchers and Cultural Creators, RETOS-MINECO (PID2020-112705RB-I00), "ERDF, A way of making Europe," La Caixa (HR22-00737), the Red Española de Investigación en Estrés/Spanish Network for Stress Research (RED2022-134191-T), and MCIN/AEI/10.13039/501100011033.

The BBVA Foundation takes no responsibility for the opinions, statements, and contents of this project, which are entirely the responsibility of its authors. In the past 3 years, Murray Stein has received consulting income from Aptinyx, atai Life Sciences, BigHealth, Biogen, Bionomics, Boehringer Ingelheim, Delix Therapeutics, EmpowerPharm, Engrail Therapeutics, Janssen, Jazz Pharmaceuticals, Karuna Therapeutics, Lykos

Therapeutics, NeuroTrauma Sciences, Otsuka US, PureTech Health, Sage Therapeutics, Seaport Therapeutics, and Roche/Genentech. He has stock options in Oxeia Biopharmaceuticals and EpiVario and has been paid for his editorial work on the journals *Depression and Anxiety* (Editor-in-Chief), *Biological Psychiatry* (Deputy Editor), and *UpToDate* (Co-Editor-in-Chief for Psychiatry). In addition, he has received research support from the NIH, VA, and DoD. He is on the scientific advisory board of the Brain and Behavior Research Foundation and the Anxiety and Depression Association of America.

ORCID

Tanja Jovanovic https://orcid.org/0000-0002-6456-0053

REFERENCES

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.).

Andero, R., Brothers, S. P., Jovanovic, T., Chen, Y. T., Salah-Uddin, H., Cameron, M., Bannister, T. D., Almli, L., Stevens, J. S., Bradley, B., Binder, E. B., Wahlestedt, C., & Ressler, K. J. (2013). Amygdala-dependent fear is regulated by Oprl1 in mice and humans with PTSD. *Science Translational Medicine*, *5*(188), Article 188ra73. https://doi.org/10.1126/scitranslmed.3005656

Andero, R., Heldt, S. A., Ye, K., Liu, X., Armario, A., & Ressler, K. J. (2011). Effect of 7,8- dihydroxyflavone, a small-molecule TrkB agonist, on emotional learning. *American Journal of Psychiatry*, *168*(2), 163–172. https://doi.org/10.1176/appi.ajp.2010.10030326

Bonne, O., Brandes, D., Gilboa, A., Gomori, J. M., Shenton, M. E., Pitman, R. K., & Shalev, A. Y. (2001). Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *American Journal of Psychiatry*, *158*(8), 1248–1251. https://doi.org/10.1176/appi.ajp.158.8.1248

Florido, A., Velasco, E. R., Romero, L. R., Acharya, N., Marin Blasco, I. J., Nabás, J. F., Perez-Caballero, L., Rivero, G., Olabarrieta, E., Nuñez-delMoral, A., González-Parra, J. A., Porta-Casteràs, D., Cano, M., Steward, T., Antony, M. S., Cardoner, N., Torrubia, R., Jackson, A. C., Fullana, M. A., & Andero, R. (2024). Sex differences in neural projections of fear memory processing in mice and humans. *Science Advances*, *10*(28), Article adk3365. https://doi.org/10.1126/sciadv.adk3365

Florido, A., Velasco, E. R., Soto-Faguás, C. M., Gomez-Gomez, A., Perez-Caballero, L., Molina, P., Nadal, R., Pozo, O. J., Saura, C. A., & Andero, R. (2021). Sex differences in fear memory consolidation via Tac2 signaling in mice. *Nature Communications*, *12*(1), Article 2496. https://doi.org/10.1038/s41467-021-22911-9

Galatzer-Levy, I. R., Ma, S., Statnikov, A., Yehuda, R., & Shalev, A. Y. (2017). Utilization of machine learning for prediction of post-traumatic stress: a re-examination of cortisol in the prediction and pathways to non-remitting PTSD. *Translational Psychiatry*, *7*(3), Article e0. https://doi.org/10.1038/tp.2017.38

Grasser, L. R., Saad, B., Bazzi, C., Wanna, C., Abu Suhaiban, H., Mammo, D., Jovanovic, T., & Javanbakht, A. (2022). Skin conductance response to trauma interview as a candidate biomarker of trauma and related psychopathology in youth resettled as refugees. *European Journal of Psychotraumatology*, *13*(1), Article 2083375. https://doi.org/10.1080/20008198.2022.2083375

Hinrichs, R., van Rooij, S. J., Michopoulos, V., Schultebraucks, K., Winters, S., Maples-Keller, J., Rothbaum, A. O., Stevens, J. S., Galatzer-Levy, I., Rothbaum, B. O., Ressler, K. J., & Jovanovic, T. (2019). Increased skin conductance response in the immediate aftermath of trauma predicts PTSD Risk. *Chronic Stress*, *3*, Article 2470547019844441. https://doi.org/10.1177/2470547019844441

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Jovanovic, T., Phifer, J. E., Sicking, K., Weiss, T., Norrholm, S. D., Bradley, B., & Ressler, K. J. (2011). Cortisol suppression by dexamethasone reduces exaggerated fear responses in posttraumatic stress disorder. *Psychoneuroendocrinology*, *36*(10), 1540–1552. https://doi.org/10.1016/j.psyneuen.2011.04.008

Maples-Keller, J. L., Jovanovic, T., Dunlop, B. W., Rauch, S., Yasinski, C., Michopoulos, V., Coghlan, C., Norrholm, S., Rizzo, A. S., Ressler, K., & Rothbaum, B. O. (2019). When translational neuroscience fails in the clinic: Dexamethasone prior to virtual reality exposure therapy increases drop-out rates. *Journal of Anxiety Disorders*, *61*, 89–97. https://doi.org/10.1016/j.janxdis.2018.10.006

Michopoulos, V., Norrholm, S. D., Stevens, J. S., Glover, E. M., Rothbaum, B. O., Gillespie, C. F., Schwartz, A. C., Ressler, K. J., & Jovanovic, T. (2017). Dexamethasone facilitates fear extinction and safety discrimination in PTSD: A placebo-controlled, double-blind study. *Psychoneuroendocrinology*, *83*, 65–71. https://doi.org/10.1016/j.psyneuen.2017.05.023

Morrison, K. E., Stenson, A. F., Marx-Rattner, R., Carter, S., Michopoulos, V., Gillespie, C. F., Powers, A., Huang, W., Kane, M. A., Jovanovic, T., & Bale, T. L. (2022). Developmental timing of trauma in women predicts unique extracellular vesicle proteome signatures. *Biological Psychiatry*, *91*(3), 273–282. https://doi.org/10.1016/j.biopsych.2021.08.003

Nievergelt, C. M., Maihofer, A. X., Atkinson, E. G., Chen, C. Y., Choi, K. W., Coleman, J. R. I., Daskalakis, N. P., Duncan, L. E., Polimanti, R., Aaronson, C., Amstadter, A. B., Andersen, S. B., Andreassen, O. A., Arbisi, P. A., Ashley-Koch, A. E., Austin, S. B., Avdibegoviç, E., Babić, D., Bacanu, S. A., … Koenen, K. C. (2024). Genome-wide association analyses identify 95 risk loci and provide insights into the neurobiology of post-traumatic stress disorder. *Nature Genetics*, *56*(5), 792–808. https://doi.org/10.1038/s41588-024-01707-9

Sawamura, T., Klengel, T., Armario, A., Jovanovic, T., Norrholm, S. D., Ressler, K. J., & Andero, R. (2016). Dexamethasone treatment leads to enhanced fear extinction and dynamic *Fkbp5* regulation in amygdala. *Neuropsychopharmacology*, *41*(3), 832–846. https://doi.org/10.1038/npp.2015.210

Segman, R. H., Shefi, N., Goltser-Dubner, T., Friedman, N., Kaminski, N., & Shalev, A. Y. (2005). Peripheral blood mononuclear cell gene expression profiles identify emergent post-traumatic stress disorder among trauma survivors. *Molecular Psychiatry*, *10*(5), 500–425. https://doi.org/10.1038/sj.mp.4001636

Shalev, A. Y., Ankri, Y. L., Peleg, T., Israeli-Shalev, Y., & Freedman, S. (2011). Barriers to receiving early care for PTSD: results from the Jerusalem trauma outreach and prevention study. *Psychiatric Services*, *62*(7), 765–773. https://doi.org/10.1176/ps.62.7.pss6207_0765

Shalev, A. Y., Peri, T., Brandes, D., Freedman, S., Orr, S. P., & Pitman, R. K. (2000). Auditory startle response in trauma survivors with posttraumatic stress disorder: A prospective study. *American Journal of Psychiatry*, *157*(2), 255–261. https://doi.org/10.1176/appi.ajp.157.2.255

Shalev, A. Y., Sahar, T., Freedman, S., Peri, T., Glick, N., Brandes, D., Orr, S. P., & Pitman, R. K. (1998). A prospective study of heart rate response following trauma and the subsequent development of posttraumatic stress disorder. *Archives of General Psychiatry*, *55*(6), 553–559. https://doi.org/10.1001/archpsyc.55.6.553

Shalev, A. Y., Videlock, E. J., Peleg, T., Segman, R., Pitman, R. K., & Yehuda, R. (2008). Stress hormones and post-traumatic stress disorder in civilian trauma victims: a longitudinal study. Part I: HPA axis responses. *International Journal of Neuropsychopharmacology*, *11*(3), 365–372. https://doi.org/10.1017/S1461145707008127

Stein, M. B., Goldin, P. R., Sareen, J., Zorrilla, L. T., & Brown, G. G. (2002). Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Archives of General Psychiatry*, *59*(11), 1027–1034. https://doi.org/10.1001/archpsyc.59.11.1027

Stein, M. B., Levey, D. F., Cheng, Z., Wendt, F. R., Harrington, K., Pathak, G. A., Cho, K., Quaden, R., Radhakrishnan, K., Girgenti, M. J., Ho, Y. A., Posner, D., Aslan, M., Duman, R. S., Zhao, H., Polimanti, R., Concato, J., Gelernter, J., … Department of Veterans Affairs Cooperative Studies Program (No. 575B), VA Million Veteran Program. (2021). Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. *Nature Genetics*, *53*(2), 174–184. https://doi.org/10.1038/s41588-020-00767-x

Velasco, E. R., Florido, A., Flores, Á., Senabre, E., Gomez-Gomez, A., Torres, A., Roca, A., Norrholm, S., Newman, E. L., Das, P., Ross, R. A., Lori, A., Pozo, O. J., Ressler, K. J., Garcia-Esteve, L. L., Jovanovic, T., & Andero, R. (2022). PACAP-PAC1R modulates fear extinction via the ventromedial hypothalamus. *Nature Communications*, *13*(1), 4374. https://doi.org/10.1038/s41467-022-31442-w

How to cite this article: Andero, R., Jovanovic, T., Stein, M. B., & Shalev, A. Y. (2024). What I was thinking/what I would do differently: Biological markers and mechanisms of mental health. *Journal of Traumatic Stress*, 1–8. https://doi.org/10.1002/jts.23083