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Raz Yirmiya: The inflammatory underpinning of depression

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Professor Raz Yirmiya stands at the forefront of research exploring how the immune system shapes mental health, leading the Laboratory for Psychoneuroimmunology at the Hebrew University of Jerusalem. His seminal discoveries transformed our understanding of depression's biological roots when he became the first scientist to demonstrate experimentally that inflammation triggers depressive symptoms. By developing sophisticated animal models and conducting careful human studies, he revealed how inflammatory challenges affect mood and cognition, illuminating entirely new perspectives on depression's underlying mechanisms. His research unveiled the essential role of brain inflammation and microglia cells in stress-induced depression, particularly documenting how interleukin-1β and microglial dynamics influence both depressive symptoms and neurogenesis. This foundational work has become an extensive exploration of novel treatments, as Professor Yirmiya leads efforts to develop innovative antidepressants that target microglial function. Beyond his research breakthroughs, he has shaped the field through leadership roles, including serving as President of the Psychoneuroimmunology Research Society and associate editor of *Brain, Behavior, and Immunity*. In this Genomic Press Interview, Professor Yirmiya reflects on his scientific journey and shares insights illuminating the personal and professional dimensions of his quest to understand depression's biological foundations.

Figure 1. Raz Yirmiya, PhD, The Hebrew University of Jerusalem, Israel.

Part 1: Raz Yirmiya – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was dedicated to playing the piano in my youth and envisioned a future as a professional musician. After high school, I joined a military entertainment band and was fully immersed in music. However, tensions within the group led us to a week of intensive psychological group dynamics. Observing the profound impact of the psychologists leading our sessions, I was captivated by their work and decided to pursue a career in psychology. I began my undergraduate studies in Psychology and joined a special honors program, which paired each student with a personal mentor and immediate lab experience. My mentor was a psychobiologist, and soon after joining his lab, I experienced the thrill of seeing our hypotheses supported by experimental results. This hands-on experience sparked my passion for science, especially Psychobiology, and set me on an entirely new path. After graduation, I decided to deepen my understanding of biology, undertaking many basic courses in math, physics, chemistry, and biology before pursuing an MSc in Physiology. During this period, I worked with diverse animal models, from cockroaches to monkeys, studying the brain-behavior relationship in each. My admiration for the brain grew with every experiment, and I knew that neuroscience was my true calling. My graduate studies in the Neuroscience program at UCLA allowed me to learn from some of the leading scholars in the field, solidifying my fascination with the brain and its connection to behavior and the multiple bi-directional interactions between the brain, behavior, and the body's physiological systems.

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

After completing my PhD, I remained at UCLA as a Postdoctoral fellow for an additional two years, working in the laboratory of Professor John Liebeskind, an esteemed pain researcher who developed a profound interest in the new field of psychoneuroimmunology. During that period,

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Prof. Libeskind, together with prominent psychiatry researchers at UCLA, including Prof. George Solomon and Prof. Herbert Weiner, and under the guidance of the journalist and scholar Mr. Norman Cousins, established the Cousins Center for Psychoneuroimmunology. I was honored to be among the first postdoctoral fellows at the Center, in which I began to identify myself as a "psychoneuroimmunologist" – a designation that has defined my career to this day. Following the postdoctoral training, I accepted an academic position in the Department of Psychology at the Hebrew University of Jerusalem. In the early 1990s, I attended the inaugural meeting of the Psychoneuroimmunology Research Society (PNIRS). That experience solidified my commitment to this field, and PNIRS has been my primary scientific community ever since. Over the years, I attended almost all of the society's yearly meetings. I contributed to its success in many ways, including serving as its president and associate editor of *Brain, Behavior, and Immunity* journal. Within my university, I have held various administrative roles. However, I am incredibly proud that more than two decades ago, I had a leading role in establishing and directing the Inter-departmental Psychobiology Program—the first of its kind in Israel—which attracts some of the best students in psychology and life sciences each year.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

In 1990, when I established my laboratory as a beginning faculty member at the Hebrew University, my research interest, similarly to the entire field of psychoneuroimmunology at that time, was focused on the influence of brain and behavior on immune functioning and resistance to cancer. However, given that my position and laboratory were in the Department of Psychology, which in my university is located on a different campus than the Life and Medical Sciences faculties, I was unsure whether I could maintain a state-of-the-art immunology and experimental oncology laboratory. Just a year later, I participated in a scientific meeting in Jerusalem and was introduced to Prof. Robert Dantzer, who shared a preprint of a review paper in which he and his colleagues coined the term "sickness behavior" – referring to the nonspecific behavioral symptoms that accompany the immune response to infection. Immediately after reading this paper, I knew this was my most enjoyable and suitable research topic. I began by characterizing the components of sickness behavior following the administration of LPS (as a model for bacterial infection) or specific cytokines, particularly interleukin-1. While conducting these experiments, I realized that the symptoms of sickness behavior bear a resemblance to the diagnostic criteria of major depression, so I began to experimentally explore whether this similarity reflects a shared mechanism. In 1996, I published the first experimental evidence linking inflammation and depression, showing that LPS produces anhedonia in rats, reflected by significant suppression of the preference for a palatable saccharin solution, as well as reduced sexual, social, and exploratory activities, which are naturally rewarding for rodents. Further reinforcing the putative mechanistic link between sickness behavior and depression, I found that chronic (but not acute) prophylactic treatment with antidepressant drugs prevented LPS-induced anhedonia and related depressive-like symptoms. Soon after this publication, I initiated studies to extrapolate and validate these findings in humans by investigating the effects of inflammatory challenges, such as vaccination or LPS administration, on mood and cognitive functioning in healthy human volunteers. For example, in a randomized, double-blind, cross-over study, we found that following LPS administration, subjects experienced a transient pronounced increase in symptoms of depressed mood and anxiety, as well as impairments in memory function. Crucially, these affective and cognitive disruptions were significantly correlated with the LPS-induced elevations in inflammatory cytokine levels. These experiments piqued my interest in the inflammation-depression nexus, which remains my favorite research focus area three decades later.

Please tell us more about your current scholarly focal points within your chosen field of science.

Most depressed patients do not have any overt inflammatory disease. However, we and others found that exposure to stress, which is the most significant trigger of depression in humans and animals, also activates inflammatory processes, particularly in the brain. Specifically, we discovered that unpredictable chronic stress elevates the levels of the cytokine interleukin-1 (IL-1) in the brain of rodents, and this elevation plays a causal role in the development of depressive-like symptoms. The finding that brain IL-1-associated depression was accompanied by activation of microglia cells, the brain's resident immune cells, led us to hypothesize that microglial activation may be the source of stress-induced IL-1 production and, therefore, the mechanism underlying depressive symptomatology in this model. Surprisingly, our early experiments revealed that prolonged chronic stress led to reduced density and degeneration of microglia instead of the expected activation. In subsequent experiments, we discovered that the effects of repeated stress exposure are dynamic, including an initial IL-1-mediated activation phase of these cells, followed by a period of apoptosis and decline. Our studies revealed that early intervention with anti-inflammatory treatments can prevent these changes and the onset of depressive-like behaviors. However, these treatments are less effective once microglia degeneration has set in. This insight has shifted my focus towards understanding how compounds that stimulate microglial activation following prolonged stress might have antidepressant effects, potentially through enhancing hippocampal neurogenesis—a key action mechanism of many antidepressants. We are particularly interested in modulating immune/microglial checkpoint mechanisms in depression. Specifically, our findings indicate that chronic stress induces the expression of several microglia checkpoint receptors, including lymphocyte-activation gene-3 (LAG3), which may be involved in the microglia decline and associated depressive-like symptoms. Indeed, blocking LAG3, whether by electroconvulsive therapy (ECT) or specific antibodies, shows significant antidepressant effects. Similarly, we are examining the role of CX3CR1, another checkpoint receptor expressed exclusively by microglia, in stress resilience and depression. In another project, we use a chemogenetic approach to identify the specific neurons in various brain regions that generate inflammation-induced depressive-like symptoms and to examine the interactions between the neurons and microglia in their vicinity.

What impact do you hope to achieve in your field by focusing on specific research topics?

My overarching aim is to harness the extensive knowledge from my research and others to accelerate the development of novel antidepressant therapeutics targeting inflammatory processes. Recognizing that both the activation and suppression of the immune system, particularly microglia, can precipitate depressive symptoms, it is clear that a universal treatment approach is insufficient. Therefore, I advocate for a shift towards personalized medicine in treating depression. This tailored approach would commence with a thorough diagnostic assessment of a patient's inflammatory profile, followed by individualized treatment plans designed to modulate the immune and microglial responses through targeted therapies. Recently, we have identified and patented several innovative microglial modulators. For conditions characterized by microglia suppression and degeneration, we are developing therapeutic strategies involving microglia stimulants, such as M-CSF and GM-CSF, and exploring the potential of microglial checkpoint inhibitors, including anti-LAG-3 and anti-CX3CR1 antibodies, as antidepressants. Additionally, we developed several formulations of cannabinoids, flavonoids, and NSAIDs aimed at treating depression linked to microglial activation. By focusing on these specific areas, I hope to pioneer advancements that improve the treatment of specific symptoms and pave the way for more precise and effective management of depression, shifting the clinical paradigm towards customized therapeutic interventions.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

A fundamental habit I developed during my academic and postdoctoral training and steadfastly maintained in my research environment is the meticulous effort to prevent my initial hypotheses from biasing the experimental design, data analyses, or interpretation of results. The risk

of unconscious bias is significant and can divert research into unproductive directions. Some of my key discoveries have emerged from results that contradicted my original hypotheses. For instance, it was unexpected to find that prolonged stress exposure can lead to exhaustion and degeneration of microglia rather than their activation. Another core value I uphold is the openness to alternative interpretations of data, actively seeking out evidence that might contradict my initial assumptions. The following is a pertinent example of this value's benefit. After finding that prolonged chronic stress leads to microglial degeneration, I told my student, Tirzah Kreisel, that maybe we should try to treat the "depressive-like" mice with a microglial stimulator, such as LPS. Tirzah paused momentarily and said, "But we already did such an experiment." She went to her office and fetched the results of an experiment we ran more than a year earlier, hypothesizing that the depressive-like responsiveness to LPS will be greater in stress-exposed animals. However, we abandoned this research project because the results contradicted our hypothesis. Following the new insight from the microglia study, we replicated this experiment, finding that LPS produces opposite effects: In normal, non-stressed animals, it produces a depressive-like condition accompanied by microglia activation and neurogenesis suppression, whereas, in chronically stressed animals (with suppressed microglia activation status), LPS paradoxically produces antidepressant and neurogenesis-promoting effects. This example emphasizes the importance of diligently revisiting and reconsidering data, especially when it challenges our expectations. Embracing this approach has not only prevented potential misdirection in my research but has also led to groundbreaking discoveries that could redefine therapeutic strategies

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

Depression is a universal condition affecting diverse populations across all cultures and regions. However, cultural, gender, socioeconomic, and other demographic factors significantly influence both the prevalence and severity of depression. These factors can also shape how inflammatory processes contribute to the development and maintenance of this condition. For example, in one of our early studies, we discovered that active vaccination led to depressive symptoms predominantly among participants from lower socioeconomic backgrounds. Despite this diversity in susceptibility, the majority of research in this area predominantly involves participants from the Western world, typically with an overrepresentation of males, individuals of white ethnicity, and those with good access to medical services.

Additionally, experimental studies in animal models of depression often utilize only male subjects. Future studies should broaden their demographic scope to include more women and participants from varied cultural and socioeconomic backgrounds to ensure that findings are truly representative and applicable universally. Addressing these disparities will not only enrich the scientific understanding of depression but also enhance the development of targeted, effective interventions. I hope to see this transformative scrutiny in the scientific community, ensuring that research endeavors are as diverse as the populations they aim to serve.

What do you most enjoy in your capacity as an academic or research leader?

In my role as an academic leader, two aspects are gratifying. First is the exhilarating moment of analyzing new experimental data and realizing that it reveals a genuinely novel and fundamental scientific truth – one that, at that moment, is known only to me. Such moments have been rare throughout my career, but the euphoria and excitement they bring are profound and enduring. They fuel my enthusiasm and motivation, sustaining my dedication to research. The second aspect I cherish is witnessing the academic growth of my students. The journey is deeply fulfilling, from their early days as research assistants to their evolution into independent researchers with impressive academic careers. I have been privileged to mentor many outstanding students, and it brings me immense joy and pride to know that the foundational skills and knowledge they acquired in my laboratory have empowered them to excel in the academic world. This ongoing legacy of learning and discovery is what I value most as a mentor and leader.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

Outside of my professional life, I cherish the time spent with my family. My wife, Nurit, and I enjoy frequent gatherings with our wonderful four children, their spouses, and our three adorable granddaughters. It is fulfilling to follow and support my children's stellar career trajectories, offering advice and resources that help them professionally and personally flourish. Nurit and I are fortunate to be part of a close-knit group of friends we consider our 'family by choice.' Over three decades, we have met at least weekly, celebrating holidays and special occasions together, embarking on domestic and international travels, and facing life challenges and sorrows. These enduring friendships are a cornerstone of our social life, offering immense joy and support. My passion for music remains a significant part of who I am. As a pretty good amateur pianist who once played semi-professionally, I cherish this form of expression, although I hardly found time to practice in the past few decades. I am excited about dedicating more time to my musical pursuits, exploring new compositions, and collaborating with other musicians.

Part 2: Raz Yirmiya – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?

For me, perfect happiness is the profound sense of fulfillment that comes from knowing my actions have positively impacted my life and those of my family, friends, and the broader society. This kind of happiness often requires substantial time and effort, but precisely, this investment brings deep meaning, contentment, and satisfaction to my existence. The interconnectedness of my efforts with my well-being and the welfare of others is what truly defines perfect happiness for me.

What is your greatest fear?

My greatest fear is the prospect of becoming incapacitated, disabled, and dependent on others. Throughout my life, I have always strived to excel in almost everything I undertake, sometimes even avoiding activities where I felt less adept. This drive stems from a deep-seated aversion to feeling helpless or pitiable. As I contemplate the aging process, the idea of losing my independence and becoming reliant on others is particularly daunting. However, this fear also serves a constructive purpose—it motivates me to maintain excellent physical fitness and to lead a well-balanced life that integrates work and leisure. This proactive approach alleviates my fears and enhances my overall well-being, ensuring I can live fully for as long as possible.

[1]In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

Figure 2. Raz and Nurit Yirmiya explore Antarctica's stunning seascape aboard an expedition boat, with sea ice and their cruise ship visible in the misty background. The image captures a moment from their unforgettable polar expedition, which they shared with a group of good friends, set against the pristine backdrop of floating ice sheets and clear blue Antarctic skies.

Which living person do you most admire?
One living person I greatly admire is Richard Dawkins, a distinguished evolutionary biologist and author. His seminal scientific works profoundly contributed to the theory of genetic evolution via natural selection, a cornerstone of biology and our understanding of life. Beyond his scientific contributions, Dawkins is a vocal advocate for science and reason, consistently challenging religious dogma and fanaticism. His ability to articulate complex ideas with clarity has not only popularized scientific thought but also fostered broader public engagement and critical discourse on the essential role of science in society.

What is your greatest extravagance?
My greatest extravagance is my love for travel. Over the years, I've had the privilege of visiting nearly half of the world's countries, exploring every continent, including unique and exotic locales such as Lapland, Patagonia, French Polynesia, and Antarctica, as well as countless islands across the Oceans and the Mediterranean Sea. This passion for exploration has been a perfect leisure activity, but it also serves as a profound source of inspiration and learning that enriches my understanding of the world.

What are you most proud of?
I am most proud of my four children, who have grown into kind, responsible, and conscientious individuals. They are incredibly bright and highly successful in their respective endeavors, embodying qualities that any parent would be proud of. I also take great pride in the achievements of the students who have graduated from my laboratory, most of whom have become leading scientists at respected academic and medical institutions. Beyond my family and mentees, my professional contribution to understanding the biological basis of depression is a source of great pride. It is immensely gratifying to know that my work has been

instrumental in paving the way for developing novel and effective antidepressants based on immune-modulating compounds, particularly for those who do not benefit from current therapeutics.

What is your greatest regret?
My greatest regrets were the periods during my career when I diverged from my primary research focus on the inflammation-depression nexus to explore other interesting but unrelated topics. These explorations included studies on the effects of alcohol, cannabis, and cannabinoids on brain-behavior-immune interactions and the role of inflammatory processes in Alzheimer's disease. While these diversions were intellectually fulfilling and broadened my understanding of related fields, I sometimes reflect that maintaining a more singular focus on depression and inflammation could have accelerated my progress toward developing much-needed therapeutic solutions for depressed patients.

What is the quality you most admire in people?
Generosity and kindness.

What is the trait you most dislike in people?
Violence and cruelty.

What do you consider the most overrated virtue?
While industriousness is often celebrated as a key driver of success and productivity, it can sometimes be overrated, especially when it leads to work overshadowing other essential aspects of life. In academic life, the emphasis on being perpetually active can discourage creativity and strategic thinking, which require time for reflection and rest. Therefore, while industriousness is valuable, it is crucial to balance it with periods of rest and rejuvenation to maintain long-term productivity and well-being.

What are your favorite activities?
Playing the piano and cycling.

Where would you most like to live?
I love my home. I would not like to live anywhere else.

What is your most treasured possession?
My most treasured possessions are not material but define my deep connections with my family and friends. My loving relationships with my wife, children, and granddaughters are irreplaceable and provide me with immense joy and support. Similarly, my decades-long comradeship, characterized by deep bonds with a close group of friends, is something I hold very dear. These relationships enrich my life far beyond what any physical object could, underscoring the belief that loving and supportive connections are the most valuable possessions one can have.

When and where were you happiest? And why were so happy then?
Reflecting on my life, I realize I have been the happiest since the beginning of my sixth decade. After navigating numerous challenges in my childhood, adolescence, and early adulthood—each challenging for different reasons—it was during these later years that all aspects of my life began to stabilize and flourish. Personally, professionally, financially, and socially, I found a harmonious balance that has progressively increased my happiness. This period of stability and contentment continues to deepen with time, so I am at the peak of my well-being.

What is your current state of mind?
Currently, I am in a state of mixed emotions. I am content and fulfilled, grateful for the happiness and joy in my life. However, deep concerns about my country's ongoing political and social challenges overshadow my sense of peace. The threat of moving towards an autocratic system with fascist and ultra-religious characteristics is particularly alarming. Despite these troubles, I remain hopeful that reason and moderation will prevail and that we will return to a more balanced and democratic governance.

What is your most marked characteristic?
My most marked characteristic is commitment. This dedication permeates all aspects of my life—from my family and friends to my students and scientific work. I am deeply committed to the welfare and success of those around me, as well as to advancing our understanding and application of science for the betterment of society. This steadfast commitment drives me to consistently strive for excellence and support others in achieving their goals.

Among your talents, which one(s) give(s) you a competitive edge?
My competitive edge in my field stems primarily from my ability to synthesize diverse knowledge—facts and concepts—into a cohesive and comprehensive understanding of the subjects I explore. This capability allows me to develop a panoramic view of complex scientific landscapes, enabling breakthrough insights and innovations. My willingness to embrace data contradicting prevailing dogmas and even my initial hypotheses is also crucial. This openness fuels my scientific creativity and fosters significant advancements in my research.

What do you consider your greatest achievement?
My most outstanding achievement is undoubtedly my groundbreaking work demonstrating the causal role of inflammation in depression through a series of pivotal studies. My initial research, published in *Brain Research* in 1996, was the first to show that an inflammatory challenge, namely lipopolysaccharide (LPS), could induce a depressive-like episode in rats. This study laid the foundation for the LPS model of depression, which has significantly influenced the field by providing a reliable method to investigate the pathophysiology of depression related to immune system dysfunction. Furthering this line of inquiry, my team and I published the first study on LPS-induced cytokine-dependent depressed mood in humans in the *Archives of General Psychiatry* in 2001. These foundational studies have since inspired over 700 subsequent research papers utilizing the LPS model of depression, significantly advancing our understanding of the biology of this disease. My subsequent research, including pivotal publications in *Molecular Psychiatry* in 2008, 2014, and 2022, pioneered exploring and establishing the critical roles of interleukin-1 in the brain and dynamic microglial alterations in chronic stress-induced depressive-like states. These contributions have not only enriched our understanding of depression but have also opened new avenues for the development of novel antidepressant therapeutic interventions based on the modulation of inflammation processes.

If you could change one thing about yourself, what would it be?
If I could change one aspect of myself, it would be my tendency toward perfectionism. While striving to excel in every activity I undertake has its merits, it often comes with relentless pressure that can be exhausting. I wish to cultivate a more lenient and forgiving attitude towards myself, balancing pursuing excellence with a healthier acceptance of imperfection.

What do you most value in your friends?
Loyalty, integrity, trustworthiness, supportive, and unjudgmental attitude.

Who are your favorite writers?
Mario Vargas Llosa, José Saramago, David Grossman, and A. B. Yehoshua.

Who are your heroes of fiction?
One of my fiction heroes is Henri Charrière's character Papillon from the autobiographical novel *Papillon*. This character embodies resilience, resourcefulness, and an indomitable will to regain his freedom against overwhelming odds. Papillon's journey is a tale of physical survival and a profound narrative of the quest for justice and the refusal to be broken by unjust circumstances. His story inspires hope and a steadfast belief in the strength of the human spirit and one's ability to overcome adversity.

Who are your heroes in real life?
My real-life heroes are the leaders and activists who courageously oppose tyranny and autocracy globally and within my country.

What aphorism or motto best encapsulates your life philosophy?
You will never be sorry for investing too much time and effort in your family, friends, and your own body

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