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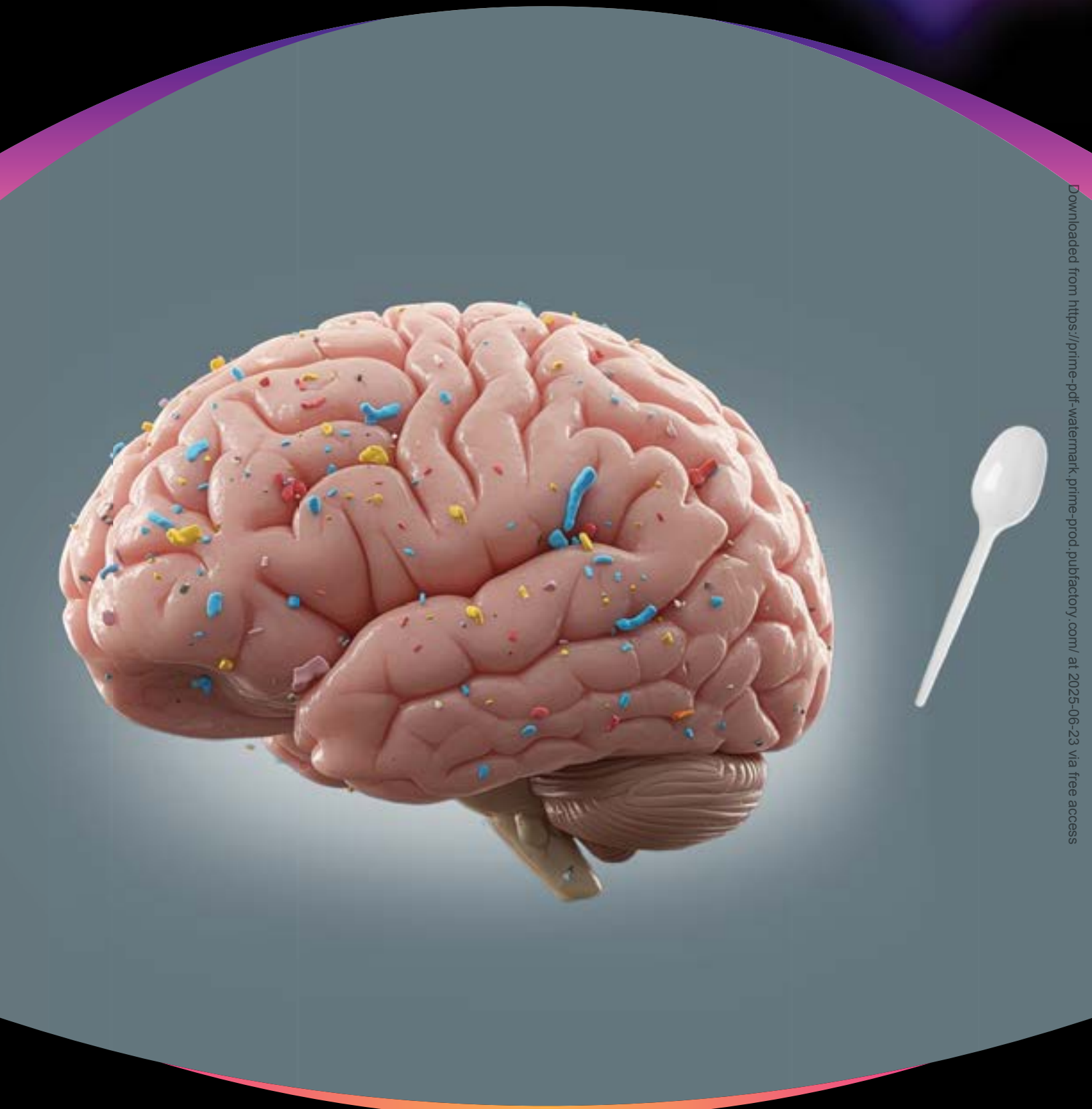
BRAIN MEDICINE

From neurons to behavior and better health



Volume 1 | Number 3 | May 2025

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2025 CONFERENCE

The Changing Brain

August 18 – 20, 2025 | Irvine, California, USA

- The Evolving Brain
- The Learning Brain
- States of the Brain
- The Developing Brain
- The Dynamic Brain
- The Disordered Brain

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Xiangmin Xu, University of California, Irvine
Liqun Luo, Stanford University
Hongkui Zeng, Allen Institute for Brain Science

Confirmed Speakers:

Ishmail Abdus-Saboor, Columbia University
Paola Arlotta, Harvard University
Carlos Brody, Princeton University
Beth Buffalo, University of Washington
Edward Chang, UCSF
Anne Churchland, UCLA
Yang Dan, University of California, Berkeley
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Brain Medicine

Table of Contents

Volume 1 • Number 3 • May 2025

Cover Art

This cover image depicts a human brain with colorful microplastic particles scattered across its surface, juxtaposed with a white plastic spoon as a visual representation of the alarming findings initially reported by Nihart et al. (*Nature Medicine*, 2025) and further analyzed by Fabiano, Luu, and Puder in this issue (pages 29–30). Research has revealed that the human brain contains approximately "a spoon's worth" of microplastics and nanoplastics, with particularly high concentrations (3–5 times greater) in individuals with dementia. The multicolored particles shown on the brain surface represent the variety of plastic types detected, with polyethylene being predominant. The image illustrates the concerning 50% increase in microplastic concentration observed between 2016 and 2024, highlighting the rapid infiltration of these synthetic materials into our most protected organ.

Image credit: Genomic Press.

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Brain Medicine

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GUEST EDITORIAL

Una cuchara de plástico en tu cerebro: The calamity of a plastic spoon in your brain

Brain Medicine May 2025;1(3):1–3; doi: https://doi.org/10.61373/bm025g.0062

A Picture That Refuses to Soften

The image on our cover was not chosen for effect. It is neither abstract nor poetic. It is not "inspired by" anything. It is an unflinching report: a human brain, stippled with bright fragments of microplastics, not imagined but real, caught at the precise intersection of scientific fact and biological intrusion. That the visual is disturbing is not a matter of aesthetics. It is a reflection of an epistemic break. The blood-brain barrier, long treated as a sacred anatomical defense line, has been crossed. We now have polymers where cognition happens.

This moment reframes more than a risk profile. It shatters a framework. For years, whispers within environmental science anticipated the encroachment. That plastics would enter our biology was inevitable, they said. But even the most pessimistic among them did not expect this: particles in the hippocampus, polymers tangled with neurons, synthetic debris within the very tissues that govern memory, identity, and mood (see Fig. 1). What was theory has been replaced by evidence. And the consequences are no longer theoretical.

Between Disciplines, Beyond Containment

This issue presents a series of papers that do not comfortably belong to a single field. Their home lies between disciplines. Toxicology, neurology, public health, and molecular biology all converge here uneasily. The work we have chosen to feature does not form a collection, not in the traditional sense. It is, instead, a confrontation. These papers reveal that materials once celebrated for their durability and convenience now reside inside our most vital organ, the brain, not metaphorically but physically.

One Spoon, One Era

Fabiano, Luu, and Puder, the authors of the featured commentary, do not begin with declarations (1). They begin with data. Their focused review looks at and expands on the findings of Nihart et al. (2), and what they uncover is not just quantitative; it is cognitively disturbing. An average of one spoonful (yes, a spoon's worth!) of microplastic particles has been identified in human brain tissue (see Fig. 1). That this number is real is difficult enough. That it is three to five times higher in individuals with dementia is something else entirely.

Levels climbed by approximately 50 percent between 2016 and 2024. That is not background noise. That is velocity.

Beyond quantification lies causation. In their broader Viewpoint on microplastics, ultra-processed foods, and mental health, Fabiano, Luu, Puder, and Marx connect the alarming rise in brain microplastics with our changing food systems (3). Ultra-processed foods—now comprising over 50% of energy intake in countries like the United States—contain exponentially more microplastics than whole foods. Chicken nuggets, they note, harbor 30 times more microplastics per gram than chicken breasts. The microwave heating of plastics releases millions of particles within minutes. Their work establishes a critical bridge between diet, environmental contamination, and potentially, our rising rates of depression and cognitive decline.

Fragility in Acceleration

But beyond the shock of the numbers is something subtler, and more troubling: temporal acceleration. An increase of that magnitude across just eight years implies not only spread but speed, a momentum that traditional public health models are not built to accommodate—a reality equally apparent in the rapid global shift toward ultra-processed food consumption documented by Fabiano and colleagues. The fact that higher concentrations were observed in dementia patients prompts a question we are not yet equipped to answer: are microplastics contributing to neurodegeneration, or does a degenerating brain become more permeable, more absorbent?

The authors do propose a path that is narrow but navigable. Their recommendations, rooted in empirical pragmatism, focus on behavioral modifications: choose tap over bottled water, refrain from heating food in plastic, and question the safety of ultra-processed foods. These are not revolutionary acts, perhaps, but they are not irrelevant either.

The Tea Bag and the Apheresis Machine

Their analysis goes further down to the specific, sometimes mundane, entry points of contamination. Tea bags release billions of submicron plastic particles during brewing. It sounds absurd, but it is not. So, we move from concept to detail, from macroecology to domestic ritual.

Then we come to removal. In an exciting Brevia, also in this issue, Bornstein et al. offer what may be the first true shift in the paradigm, from detection to extraction (4). Their work, cautious but ambitious, explores extracorporeal therapeutic apheresis to remove microplastic-like particles from the bloodstream.

The method is not new. The intention is.

Peripheral Disorders, Central Signals

Their subjects, patients with myalgic encephalomyelitis/chronic fatigue syndrome, were not arbitrarily chosen. These individuals often live at the edge of biomedical consensus. Yet it is precisely at those edges that new truths surface. Bornstein's team detected 14 distinct microplastic-like compounds in apheresis eluates. Preliminary? Yes. Disregardable? Absolutely not.

The mechanisms posited, such as inflammation, oxidative stress, and endocrine disruption, are well-known. But it is their entanglement that matters. These are not isolated insults. They are mutually reinforcing.

Profiles in Translation

Dr. Fabiano, profiled in this issue in our Innovators & Ideas section as a "Rising Star," understands disruption from within (5). His journey, from orthopedic trauma and psychiatric insight to research synthesis, reflects what this moment requires. His work on exercise as antidepressant treatment mirrors the same systems logic that microplastic pathology demands.

Highlighted in our Innovators & Ideas: Research Leaders section, Professor Bornstein's work on the HPA axis is a map of cascading failure (6).

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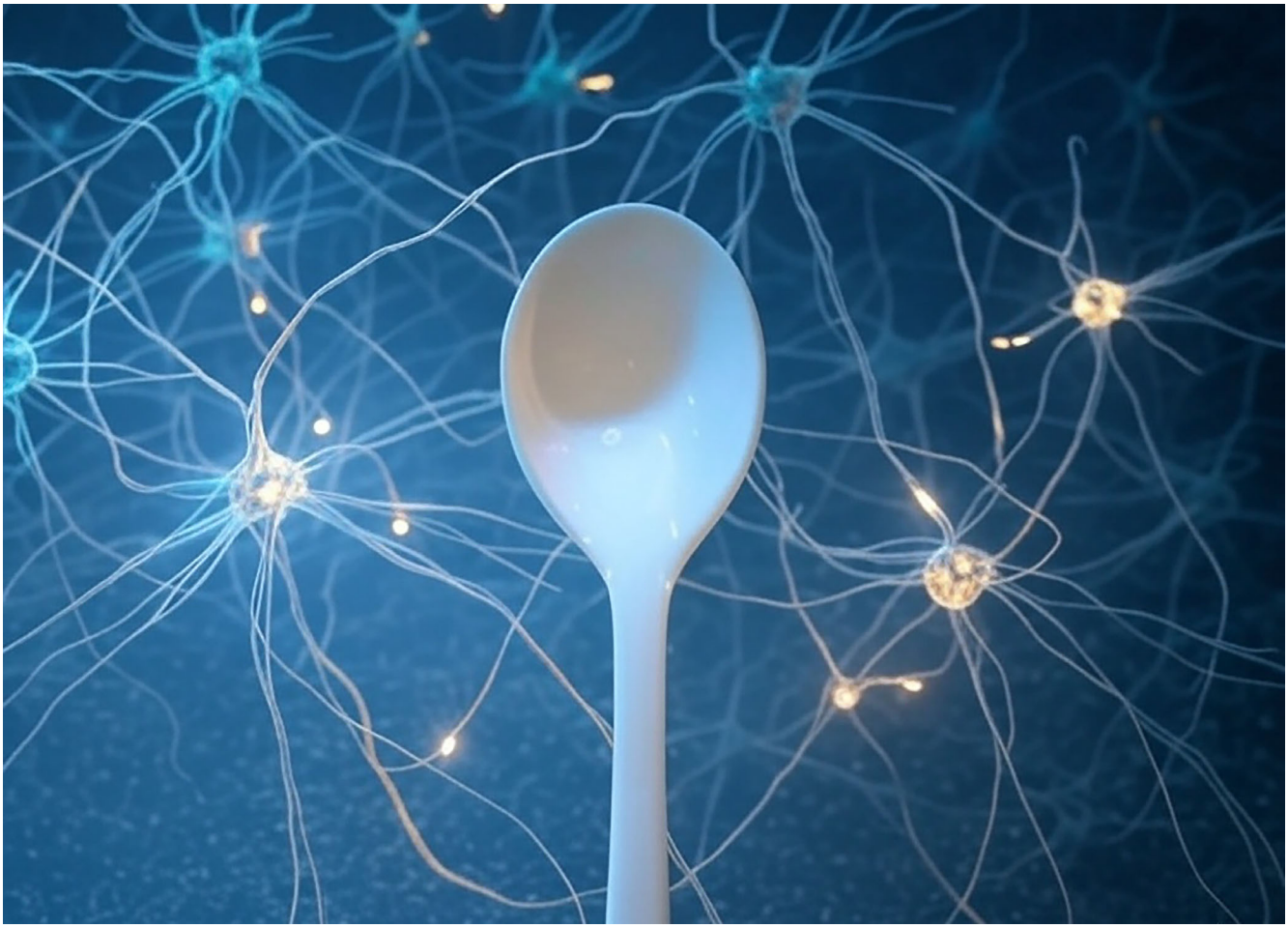

Figure 1. The plastic spoon in neural context. This visual metaphor represents the alarming findings reported by Nihart et al. (2) and further analyzed by Fabiano, Luu, and Puder (1): approximately a spoon's worth of microplastic particles has been detected in human brain tissue. A mundane object from daily life, the plastic spoon is juxtaposed against a neural network background, highlighting how synthetic materials now infiltrate our most complex organ. The glowing neurons surrounding the spoon illustrate potential sites of microplastic deposition within cerebrovascular walls and immune cells, particularly concerning given their concentration is 3–5 times higher in individuals with dementia. Image generated by Grok (xAI, 2025), with active author input.

When stress, inflammation, and metabolism collapse, the result is not just dysfunction but disintegration.

We also showcase Dr. Charlotte Steenblock as a "Rising Star" (7). Her models of stem and progenitor cells under stress show that exposure may not just harm It may reroute. Alter cell fate. Rewire development.

When Contamination Becomes Occupation of the Brain

At this point, we must stop pretending that these papers are about "risk." That language is too weak. What they document is not potential harm. It is present infiltration. The brain is not threatened. It is occupied.

What emerges from this work is not a warning. It is a reckoning. The boundary between internal and external has failed. If microplastics cross the blood-brain barrier, what else do we think remains sacred?

The Viral Spoon

And then, quickly and globally, came the response. Fabiano, Luu, and Puder's paper was not merely read. It was echoed. In twenty languages. In headlines. In memes. "Una cuchara de plástico en tu cerebro." A plastic spoon in YOUR brain. A metaphor that became too real.

Spain. South Korea. Argentina. Germany. United Kingdom. New Zealand. Canada. USA. Hong Kong SAR and China—The highest viewed Spanish-language website in the world, having surpassed 100 million unique visitors per month: *El País*. Four of the top five newspapers in Germany: *Frankfurter Allgemeine Zeitung* (FAZ), *Süddeutsche Zeitung* (SZ), *Die Welt*, *Die Zeit*. The most circulated newspapers in their countries: *Daily Mail* and *New Zealand Herald*. *National Post*. *Washington Post*. *Newsweek*. Associated Press. *Miami Herald*. *South China Morning Post*. 163.com. A million impressions within days (8).

It was not science communication. It was cultural cognition. People understood this. Deeply. Instinctively. While this viral response applies primarily to the first cited commentary on human microplastic removal, the Viewpoint by Fabiano, Luu, Puder, and Marx on microplastics, ultra-processed foods, and mental health and the Brevia on microplastic elimination by apheresis are just being published; their global outreach is rapidly building momentum.

Brain Medicine in the Present Tense

It is not incidental that *Brain Medicine* became the conduit for this message. This journal is not simply a publisher. It is a translator from data to dialogue, from research to relevance.

The brain on the cover is not symbolic. It is diagnostic. It demands we admit: the environment is inside us now.

Looking Ahead

The path forward will not be linear. We need particle detection and epidemiology, longitudinal studies, and legislative reckoning. A robust

scientific debate is currently underway among analytical experts regarding the validity of microplastic detection methodologies in human samples. From recent advancements in blood sampling techniques (9) to improved multivariate quantification using non-targeted pyrolysis GC-MS (10) and innovative biosensing approaches (11), the field is rapidly evolving. These ongoing refinements are essential as we work toward developing standardized methods that yield valid, reproducible, and reliable data, ultimately enabling evidence-based preventive strategies and medical interventions in the future.

We need to ask whether removal is possible, not in theory but in practice.

We also need to tolerate uncertainty, act before every causal arrow is known, and discard the illusion that caution means waiting.

What these papers offer is not the conclusion. It is the ignition.

They ask us to think differently.

To respond differently.

And perhaps, finally, to feel differently.

From Laboratory to Leadership

As I conclude this editorial, a striking convergence surfaces. US Health and Human Services (HHS) Secretary Kennedy's recent declaration that "Microplastics are everywhere—in our water, our soil, our food, even our organs" elevates what began as scientific observation into governmental recognition (12). RFK Jr's framing of the crisis not as "pollution" but as "market failure" echoes precisely what our researchers have documented: systems-level collapse requiring systems-level intervention. The Secretary's commitment to "fix the incentives and stop this toxic cycle" represents the policy response our findings demand. Whether through rewarding companies developing sustainable packaging or regulating chemicals near food sources, we are witnessing the rare moment when scientific alarm translates to governance action.

The plastic spoon is no longer just in our brains. It is now on policymakers' desks. What these papers initiated in laboratories may now find completion in legislation. This is how science should work: not as isolated knowledge, but as catalyst for correction. The environment inside us has finally become visible to those with the power to protect it.

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INNOVATORS & IDEAS: RISING STAR

Nicholas Fabiano: Removing the divide between physical and mental health

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Keywords: Mental health, physical health, lifestyle psychiatry, science communication

Emerging researcher Nicholas Fabiano, a psychiatry resident at the University of Ottawa, is committed to bridging the historical divide between physical and mental health. After a broken bone from arm wrestling that required surgical repair and led to nerve damage, he discovered firsthand how physical trauma impacts mental wellbeing – and how exercise can aid recovery of both body and mind. Dr. Fabiano's journey sparked his research into lifestyle interventions for mental health, with a focus on the therapeutic potential of exercise for depression. His recent work includes meta-analyses on exercise and suicide risk alongside practical frameworks helping clinicians "prescribe" exercise for patients with depression. Through active science communication and interdisciplinary collaborations spanning nephrology, cardiology, and ophthalmology, Nicholas advocates for an integrated approach recognizing the profound interconnection between physical and mental wellness. In this Genomic Press Interview, he reflects on his path in medicine, challenges the artificial separation of mind and body, and shares evidence-based guidance for implementing lifestyle interventions in psychiatric care.

Figure 1. Nicholas Fabiano, MD, University of Ottawa, Canada.

Part 1: Nicholas Fabiano – 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 have always been obsessed with figuring out how things worked. When I was younger, I would take toys and electronics apart to understand their inner workings. My parents used to tell me that I would approach family friends and always ask if they wanted to do "science experiments". This passion continued throughout my early years in school, where I watched science videos on YouTube, such as Veritasium and Vsauce, for hours on end. I wanted to learn everything I could about biology, chemistry, and physics – I could not choose a single discipline to focus on.

Due to my numerous interests, I decided to pursue a university degree where I could study disciplines across the scientific spectrum rather than limiting myself to a specific niche. As such, I pursued an Applied Life Sciences degree at Lakehead University in my hometown, Thunder Bay, Ontario, Canada. In my first year of University, I was recruited to work in a lab led by Dr. Stephen Kinrade, whose research focused on the chemistry and biochemistry of silicon, including applications in materials science, health, and agriculture. My project was titled "Production of Silicon-31 Radiotracers for the Purpose of Autoradiographic Imaging". Essentially, I developed a novel framework for an isotope production protocol using the product neutrons from the O-18[p,n]F-18 reaction used in the production of radiopharmaceuticals; the P-31 developed silicon-31 [n,p]Si-31 reaction using fast neutrons, which was used to image path and accumulation of silicon within plants. In simple terms, I was taking X-rays of plants to see where silicon accumulated. This project was perfect for so many reasons. Firstly, it was a combination of biology, chemistry, and physics; all of my passions were in one project. Second, I had no idea what I was doing – at first. This might sound wild, but my favorite part of science is the unknown. It forced me to learn new terms, read novel papers, and apply what I learned in real-time.

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

Continuing from my imaging of plants, I decided that it would make sense for me to continue my career in radiology. As such, I began to do research with an outstanding preceptor, Dr. Matthew McInnes, where I learned about radiology and the intricacies of publication bias, outcome reporting bias, spin, and citation bias on the evidence base. However, as I went through medical school, I found that what interested me the most was not looking at brain scans but instead the mind's inner workings.

Looking back, it was clear. Throughout my medical rotations, I was much more fascinated by how a patient's physical illness may impact their mind – and vice versa. I wanted to get to know all of my patients as people beyond their medical labels. It was not until near the end of medical school that I completed my first psychiatry rotation. I worked with two excellent preceptors, Dr. Jess Fiedorowicz and Dr. Andrew Smith, during an inpatient psychiatry rotation, which confirmed that this was the specialty for me. I was so fascinated by the various manifestations of the

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mind – from depression to mania to psychosis. I found myself going home and reading for hours each day out of pure interest and curiosity. I immediately switched all my final year electives to psychiatry and was fortunate to match my first choice at the University of Ottawa for my psychiatry residency. I then began to focus my psychiatry research with my outstanding supervisors, Dr. Marco Solmi and Dr. Jess Fiedorowicz.

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

I have always held the belief that the arbitrary line we have drawn between mental and physical health is one of the biggest mistakes in medicine. Coupled with my personal experiences of weightlifting, competitive soccer, and a broken arm from arm wrestling, I became very interested in lifestyle (exercise, diet, and sleep) approaches to mental health. I noticed that throughout medical school and residency, emphasizing my exercise, diet, and sleep habits improved my mood, decreased anxiety levels, and significantly improved my academic performance. This became abruptly apparent when I broke my arm while arm wrestling in my first year of medical school. Suddenly, I was unable to do the things that I enjoyed so much, and it had significant negative impacts on my overall mental state – influencing all aspects of my life. Not only had I fractured my arm, but during the surgical repair, my radial nerve was damaged, leading to a loss of sensation and motor function, and it was unclear if this would ever return. This was overwhelming for me, as I worried that I would never be able to do the things I had enjoyed or return to a healthy physical state. Due to my lack of activity and physical deterioration, I immediately felt the impact on my mental state, mood, and anxiety levels. However, after a few weeks, I went back to the gym (with my arm still in a sling) and began to train, more motivated than ever. After a few months, I had regained most of my motor function and nerve function, and I was in a significantly better mental state. I used this motivation to propel me to levels that I had not even been at pre-injury, and this truly inspired my research on both the overlap between mental and physical health and also on the potential for exercise as a treatment for depression.

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

The main goal that I wish to achieve in my field is to remove the divide between mental and physical health. They are significantly intertwined and influence one another in a multitude of ways. By ignoring one's physical health, you are not thoroughly treating their mental health and vice versa. As such, I have conducted numerous projects with departments outside of psychiatry (such as nephrology, cardiology, and ophthalmology, among others) to foster collaboration between fields more traditionally seen to operate in isolation. A more focused interest that is indirectly aimed at removing the divide between mental and physical health is my passion for exercise, diet, and sleep as a treatment for mental disorders. I hope to contribute to the evidence base for their use across disorders and provide guidance for physicians looking for assistance on "prescribing" these lifestyle measures.

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

Currently, my main interest is exercise as a treatment for depression. I have recently published a paper that corrected the misleading headline that "exercise is 1.5 times more effective than medication or cognitive behavioral therapy," which was widely disseminated to millions across news outlets, podcasts, videos, and blogs (Fabiano et al., *Journal of Physical Activity and Health, 2024*). I have also conducted two meta-analyses (Fabiano et al., *Journal of Affective Disorders, 2023*; Fabiano et al., *Neuroscience & Biobehavioral Reviews, 2024*), which demonstrated that exercise was associated with a reduction in suicide attempts; however, they found no association with suicidal ideation or deaths by suicide. Initially, it was postulated that this occurred since exercise is known to reduce emotional impulsivity. However, I have since written a piece titled "Is exercise a form of self-harm" (Fabiano et al., *Sports Psychiatry, 2024*) which reframed this discussion from a novel perspective. In this article, I postulated that in some instances, exercise may serve as a socially acceptable form of self-harm, which may explain the observed decrease in self-harm and suicide attempts following exercise in my previous work. This has generated significant online discussion and resulted in some primary studies examining my hypothesis. Beyond this, I noticed that there was a significant gap in terms of guidance in terms of prescribing exercise for depression. Thus, I recently published a framework for physicians to follow when discussing exercise "prescriptions" for depression with their patients (Zhou et al., *Sports Psychiatry, 2024*).

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

Not being afraid to be incorrect. During my early research days, I was afraid to share my ideas or thoughts publicly, fearing being wrong and scrutinized. However, I soon realized that being incorrect is completely okay, leading to greater discussion and discoveries.

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?

There is a growing inaccessibility of science. According to the most recent estimates, between 2019 and 2023, researchers had to pay nearly USD 9 billion to have their work open access and freely accessible. This creates a barrier to open science and, more importantly, inequality for those without the outrageous funds to publish.

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

The ability to approach a gray area with confidence and curiosity. In psychiatry specifically, there are so many unknowns, which allows me to attempt to answer infinite questions.

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?

While alone: lifting weights while listening to music. While with friends and family: at the cottage fishing or kayaking.

Part 2: Nicholas Fabiano – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?

A healthy body and mind.

[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.

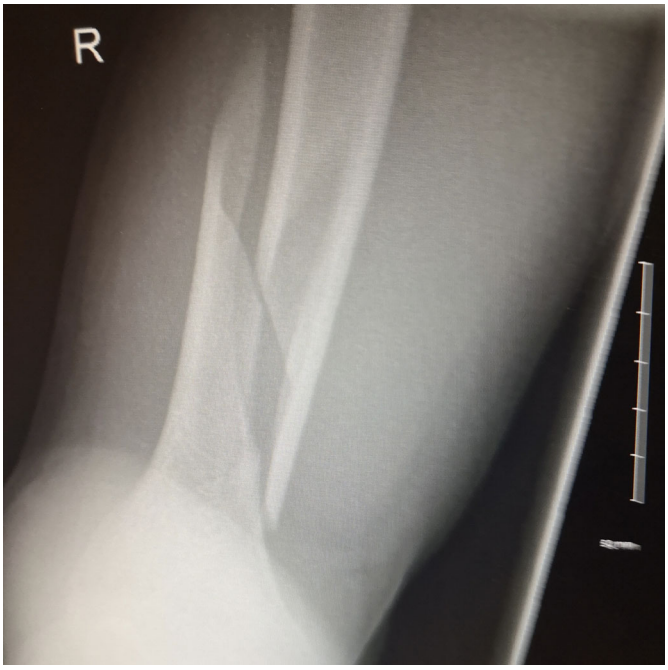

Figure 2. A pivotal moment captured in black and white – the X-ray of my fractured humerus from an ill-fated arm-wrestling match. While not my proudest moment, this break became an unexpected catalyst for my exercise and mental health research. It is funny how life works – what started as a rather embarrassing injury in my first year of medical school became a profound lesson about the mind-body connection and sparked my entire research direction. For those curious about the "before" that led to my current work in lifestyle psychiatry, this image tells the story better than words can.

What is your greatest fear?
To look back and regret not having done something because I was afraid.

Which living person do you most admire?
Roger Penrose.

What is your greatest extravagance?
Will look into that once I pay off my student debts.

What are you most proud of?
My friends and family.

What is your greatest regret?
Nothing, since everything is a learning opportunity.

What is the quality you most admire in people?
Grit.

What is the trait you most dislike in people?
Arrogance.

What do you consider the most overrated virtue?
Intellect, as it will never replace hard work.

What is your favorite occupation (or activity)?
Fishing on the lake with my family.

Where would you most like to live?
On the lake at my cottage.

What is your most treasured possession?
The plate and screws that hold my arm together.

When and where were you happiest? And why were so happy then?
Today. I feel so fortunate to be in my current place in life, surrounded by so many great people. I am also so excited by the numerous opportunities that await me, which I work so hard towards each and every day.

What is your current state of mind?
Perpetually curious.

What is your most marked characteristic?
Dedication.

Among your talents, which one(s) give(s) you a competitive edge?
I am not afraid to be wrong or embarrass myself, which leads to fruitful discussions, new ideas, and extensive learning opportunities.

What do you consider your greatest achievement?
Overcoming the mental and physical hardships after breaking my arm and sustaining nerve damage.

If you could change one thing about yourself, what would it be?
I am constantly trying to improve by looking up to people who inspire me.

What do you most value in your friends?
Loyalty.

Who are your favorite writers?
My latest read was Brain Energy by Chris Palmer.

Who are your heroes of fiction?
Rock Lee.

Who are your heroes in real life?
My parents.

What aphorism or motto best encapsulates your life philosophy?
Hard work beats talent when talent does not work hard.

Ottawa, Ontario, Canada
17 February 2025

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INNOVATORS & IDEAS: RISING STAR

Charlotte Steenblock: How does stress impact stem cells of the hypothalamic-pituitary-adrenal axis?

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Keywords: Adrenal, stress, hypothalamic-pituitary-adrenal axis, metabolic diseases, endocrine diseases, cell therapy

Dr. Charlotte Steenblock is a group leader at the Department of Internal Medicine at the Carl Gustav Carus University Clinic in Dresden, Germany. Her research focuses on stem and progenitor cells of the hypothalamic-pituitary-adrenal axis. Using animal models of physical and metabolic stress, she investigates the role of different kinds of stress on the proliferation, differentiation, and migration of these stem and progenitor cells. Furthermore, she aims to differentiate pluripotent stem cells into steroid-producing adrenal cortex-like cells that can ultimately serve as cell replacement therapies for patients suffering from adrenal insufficiency or congenital adrenal hyperplasia. Lastly, Dr. Steenblock researches the connections between metabolic and endocrine diseases and infectious diseases, including post-acute infectious syndromes such as long-COVID. Dr. Steenblock is happy to answer the Genomic Press Interview, providing our readers with reflections on her life and career.

Part 1: Charlotte Steenblock – 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 born and raised in a small city in Denmark near the German border. I have always had a passion for math, and during high school, I was fortunate to have an excellent chemistry teacher who sparked my interest in science. However, when deciding what to study, I was concerned that focusing solely on math or chemistry might feel too dry. Instead, I chose to study chemistry and molecular biology at Aarhus University in Denmark. To my surprise, I found molecular biology even more captivating than math and chemistry, which led me to pursue further studies.

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 graduate studies, I began my first postdoctoral position at the University of Southern Denmark. Shortly thereafter, I met my German husband. Together, we relocated to Germany, where I worked at various research institutions before landing in my current position.

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

In high school, I had to write a major report on adrenaline, which sparked my interest in the adrenal system. Despite taking a somewhat winding path in my academic career and exploring various research areas, I ultimately found a way to merge my fascination with stem cells and my interest in stress and the adrenal gland.

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

I hope to gain more insight into the mechanisms of how stress can lead to epigenetic changes that may affect individuals for the rest of their lives, potentially leading to conditions such as mental illness, heightened susceptibility to infections, and even cancer.

Figure 1. Charlotte Steenblock, PhD, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Germany.

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

Currently, my team of researchers and I are focused on studying the impact of stress on adrenocortical progenitors. We utilize mice as experimental models to achieve this, allowing us to lineage trace the progenitors. These mice are subjected to various stressors, including physical stress and metabolic stress induced by a high-fat diet or different models of type 1 diabetes. Alongside examining the migration and differentiation of adrenocortical progenitors, we explore the underlying mechanisms and signaling pathways activated in these stress models.

In another project, we differentiate mouse embryonic stem cells into steroid-producing adrenocortical cells in vitro. We then assess the

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survival and functionality of these differentiated cells in vivo by transplanting them into mouse models of adrenal insufficiency.

In recent years, amid the COVID-19 pandemic, we investigated the impact of metabolic and endocrine diseases on susceptibility to infection and the development of Long-COVID.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
During my academic training, I have learned the significance of planning to meet all deadlines. Moreover, teamwork and collaboration are indispensable for achieving any objectives.

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?
I concur with this perspective. Science must remain free from influence derived from the reputation of institutions, the volume of grants received by principal investigators, or their prominence in the field. Evaluation of scientific endeavors should be grounded in their inherent merit, rigorous methodology, and equitable interpretation.

What do you most enjoy in your capacity as an academic or research rising star?
The freedom to develop and explore one's own scientific hypotheses, collaboration with fellow scientists, and the privilege of educating and mentoring new trainees are all integral aspects of scientific endeavor.

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?
I enjoy doing sports and reading fiction, spanning genres from crime and historical novels to love stories. I also have a passion for traveling and watching good movies. I love to be with my family and friends.

Part 2: Charlotte Steenblock – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Finding a healthy balance between work, leisure, family, and personal time is essential for my well-being and happiness.

What is your greatest fear?
My greatest fears revolve around the health and well-being of my family members. Otherwise, I am generally open-minded and unafraid of new experiences.

Which living person do you most admire?
There are only so many persons I would like to name here without one single person standing out.

What is your greatest extravagance?
Traveling.

What are you most proud of?
My three sons, who are all amazing individuals in their unique ways.

What is your greatest regret?
Typically, I say that I have no regrets!

What is the quality you most admire in people?
Honesty and a sense of humor.

What is the trait you most dislike in people?
Dishonesty.

What do you consider the most overrated virtue?
Modesty.

What is your favorite occupation (or activity)?
Reading, traveling, and spending time with the family.

Where would you most like to live?
I enjoy living in Germany, but at times, I miss my family and friends back in Denmark.

What is your most treasured possession?
My memories.

When and where were you happiest? And why were so happy then?
I have had many unforgettable moments in life. To name a few, there is the day I met my husband and the birth of our children. Additionally, my experiences while traveling around the world hold a special place in my heart. I love exploring new places and experiencing different cultures.

What is your current state of mind?
Excellent – it is spring, and the sun is shining!

What is your most marked characteristic?
I have a very positive mindset.

Among your talents, which one(s) give(s) you a competitive edge?
Efficiency and organizational skills.

What do you consider your greatest achievement?
My scientific career and to manage settling in a different country.

If you could change one thing about yourself, what would it be?
To be more extroverted.

What do you most value in your friends?
Their loyalty.

Who are your favorite writers?
So many good authors are out there, so I cannot mention just a few.

Who are your heroes of fiction?
I do not have any.

Who are your heroes in real life?
My grandmothers were remarkable women. One pursued a career in pharmacology in the late 1930s because her father believed she should have the same opportunities as her brothers. Although the other grandmother wished to pursue further studies, she faced financial constraints.

[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.

Nonetheless, she made the most of her life and always remained well-informed.

What aphorism or motto best encapsulates your life philosophy?
Stop taking things so seriously. Everything will work out.

Charlotte Steenblock[1]
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INNOVATORS & IDEAS: RESEARCH LEADER

Stefan R. Bornstein: Stress, diabetes, and depression

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Keywords: stress, diabetes, depression, adrenal gland, sympatho-adrenal system

Professor Stefan Bornstein currently serves as the Chair of Medicine at the University of Dresden, Germany and Transcampus Dean at King's College London, UK. His extensive experience in the United States and Europe has equipped him with unparalleled expertise, particularly in diabetes and endocrinology. Professor Bornstein has authored over 700 publications, garnering more than 100,000 citations with an impressive h-index above 120. His work is frequently featured in journals such as the *New England Journal of Medicine*, *Nature*, and *Science*. Professor Bornstein's contributions extend beyond academia into influential leadership roles, such as founding the first European Transcampus between King's College and the University of Dresden and initiating the German Australian Institute of Translational Medicine. His achievements have earned him numerous awards, including the Order of Merit of Germany (Bundesverdienstkreuz 1. Class), the highest state distinction in Germany, the Medal of Honour of the University of Dresden, and membership in both the European and German Academies of Sciences. In 2023 Professor Stefan Bornstein became a member of the Freedom of the City of London, in recogntion of both his individual contributions and the success of the TransCampus project. Honorary citizenship of London has existed since the 13th century and originally enabled recipients, who were also required to join a Livery company, to carry out their trade in London. Whilst this practical element no longer applies, the City of London has maintained the Freedom as a living tradition. These accolades reflect his exceptional contributions to medical science and education. We are privileged to share Professor Bornstein's answers to the Genomic Press Interview with our readers.

Figure 1. Stefan R. Bornstein, MD, PhD, FRCP, MAE, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Germany.

Part 1: Stefan R. Bornstein – 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 raised in Europe in a family with diverse backgrounds in the aftermath of the Second World War. My life has been influenced by the history of my parents and grandparents, who suffered from being persecuted in the Nazi era, because they were Jewish. On the other hand, I was raised in a mountain area in the southern part of Germany, one of the most beautiful areas of Europe. My fascination for medicine and research was raised early by a passion for nature, biology, and the understanding of the complex systems in the human body. I had the opportunity to study medicine in different countries, including Germany, Israel, the United Kingdom, and the United States, which provided me early points with the advantages and challenges of learning from different educational systems. Early on, and especially with my late first wife, Monika Ehrhart-Bornstein, a prominent basic scientist in neurobiology, I learned to develop an interest in bridging various disciplines. Falling in love with the hypothalamic-pituitary-adrenal system and its interactions with the sympatho-adrenal system helped me to focus on an area bridging the complex and integrating interaction of metabolism, hormonal regulation, the brain, and the cardiovascular system. My entire career has benefitted tremendously from understanding and living the complex cybernetic models of positive and negative feedback regulation in endocrine systems. Understanding the micro-milieu and microenvironment of cells in organs and entire organisms helped me establish and develop new gene and cell therapy therapies.

In addition to giving new direction to a scientific field and establishing new diagnostic and therapeutic pathways, I was particularly fascinated by building academic structures in science and medicine. One of these structures includes a new strategic partnership among European universities, comprising excellent institutions such as the King's College in London, Technical University in Dresden, and the ETH in Zurich, among others. This model of transCampus received wide recognition and helped to force meaningful research collaborations, new interdisciplinary comprehensive research centres, and the training of MD and PhD students. I have always found my career's most rewarding and exciting to dedicate time and energy to helping my patients and opening doors for the next generation.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channelled you toward that leadership responsibility?

It was tough to decide whether to accept an endowed chair on a narrow topic like adrenal cancer in a prominent US University or the position of chair of medicine with a large faculty and broad responsibility in a less prominent German University. However, there is no right or wrong in these

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decisions: you have to listen to your gut feeling and your inner voice. You can do it if you are dedicated, motivated, and convinced of yourself!

Please share with us what initially piqued your interest in your favourite research or professional focus area.
Endocrine stress regulation represents a complex understanding of basic physiology and clinical medicine. Therefore, it helped me develop an integrated view of biomedicine.

What impact do you hope to achieve in your field by focusing on specific research topics?
My ultimate goal is to translate my work to the patient, the clinic, and society.

Please tell us more about your current scholarly focal points within your chosen field of science.
Undoubtedly, we all have to learn to use, manoeuvre, and master the challenges and advantages of artificial intelligence (AI) for our future work. This involves diagnostics, advanced therapy, daily care, and maintenance of high standards with more limited personnel.

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

At Genomic Press, we prioritize fostering research endeavours 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?
Making a difference in modern medicine requires integrating cultural and ethnic differences. As we have learned in the pandemic, acknowledging the fact that we are living in a global village where a disease or virus does not respect any borders, while at the same time understanding the biology of different genetic backgrounds remains an exciting task for the future.

What do you most enjoy in your capacity as an academic or research leader?
If you concentrate on your success, you promote only one career. However, if you promote your students, staff, and colleagues, you truly build a legacy.

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?
In nature, with friends and family.

Part 2: Stefan R. Bornstein – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
The perfect notion of happiness remains for me to look back on an interesting and productive life and say I found satisfaction and joy in what I have been doing.

What is your greatest fear?
My greatest fear is clearly to live longer than my children.

Which living person do you most admire?
Historically, the most impressive person for me is King David, a self-made man who was not afraid of anything and even of challenges that he could not expect to overcome but who captured a sense of love, music, and passion. The living person I most admire is my dear colleague Andrew Schally, one of the Nobel Prize winners in Physiology or Medicine who, even in his advanced age, keeps his energy and passion for his work and for science.

Figure 2. Stefan Bornstein skiing in the Alps.

What is your greatest extravagance?
Indeed, I have remained a child throughout my entire adulthood to this day.

What are you most proud of?
I have the capacity and strength to reinvent myself and look into the future positively.

What is your greatest regret?
I have a few regrets, but there are too few to mention.

What is the quality you most admire in people?
Keeping a positive spirit and persistence.

What is the trait you most dislike in people?
Procrastination.

What do you consider the most overrated virtue?
Always stay within the rules, especially if it becomes evident that they are inappropriate.

[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.

What is your favourite occupation (or activity)?
Skiing in the deep powder of fresh, untouched slopes in the high alpine mountains (see Figure 2).

Where would you most like to live?
In a mountain cottage.

What is your most treasured possession?
My wife, Nitzan, and my family.

When and where were you happiest? And why were so happy then?
The rare moments are when the entire family and best friends come together in a good spirit and time.

What is your current state of mind?
My wife always says that I am the only person she knows who changes from a depression-like state to a mania-like state within 15 minutes.

What is your most marked characteristic?
A continuous ability to move forward and keep a drive and passion for new challenges and ideas.

Among your talents, which one(s) give(s) you a competitive edge?
I have a gift for languages and have become multilingual, achieving fluency in several languages. This skill provides me with a distinct advantage in our era of global collaborations. Additionally, I have the capacity to grasp complex and unconnected relationships in science and beyond rapidly and then provide a clear synthesis.

What do you consider your greatest achievement?
Bringing together disciplines, fields, and ideas across institutions and national borders.

If you could change one thing about yourself, what would it be?
Being more patient.

What do you most value in your friends?
Loyalty.

Who are your favourite writers?
The Bible. Johann Wolfgang Goethe. And Heinrich Heine.

Who are your heroes of fiction?
Frank Kafka and Daniel Silva.

Who are your heroes in real life?
I do not have any heroes in real life because heroes die too early.

What aphorism or motto best encapsulates your life philosophy?
I am impressed by Shimon Peres's aphorism in his biography: "You are young as long as your ambitions for the future are bigger than your memories of the past."

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INNOVATORS & IDEAS: RESEARCH LEADER

Michele T. Pato: Nature and nurture are essential to living the fullest and most enjoyable life; it is never just about our genes but what you do with them and what you bring to the table

Brain Medicine May 2025;1(3):13–15; doi: https://doi.org/10.61373/bm024k.0016

Keywords: genomics, schizophrenia, bipolar disorders, African-American, Latino, women in science

Michele T. Pato, MD, is Professor of Psychiatry and Inaugural Director of the Rutgers Center for Psychiatric Health and Genomics. Dr. Pato's research has been focused on increasing the representation of minority populations in large-scale genomic studies and through that process further contributing to the elucidation of the genomics of common and complex psychiatric disorders, such as schizophrenia and bipolar disorders. Underrepresented minority groups, particularly those in US-based communities of Latino and African descent, have traditionally not been sufficiently included in genomic studies. Yet, these populations have the most significant disparities in health care and outcomes; they also have the potential to substantially broaden our knowledge of human genetics. Dr. Pato has a lifelong history of exposing and mentoring trainees towards pathways in research. She is the author of *NERVE: A Physician Turned Patient and Her Courageous Recovery from Traumatic Brain Injury,* published by Springer in 2023. We are delighted to present to our audience insights into Dr. Pato's life and professional journey.

Part 1: Michele Pato – Life and Career

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

A child's first words are often "*Mommy*" and "*Daddy*." I hope my parents were not too disappointed, but my first word was probably "*WHY?*" From my earliest years, I can remember being curious and constantly asking why. It was easier for my Dad, the engineer, than my Mom, the artist, to explain this, but they both did it in their own way. I won my first science fair in second grade, where I built an electromagnet. A boy in my grade had built one too, but my explanation of how it worked won me first place! It was hard being a girl and wanting to be a scientist. When I graduated from public high school in 1974, I was one of only two girls over a 10-year period to graduate first in the class. College at Brown University was all about math and science until I discovered how little we knew about how the brain worked. My major and honors thesis was in cognitive psychology. How did we think? How did we learn? So, it only seemed natural to go to medical school and become a psychiatrist. This allowed me to study the brain, which I have been doing throughout my entire professional life.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

What has always compelled me forward is teaching others. Be they patients, colleagues, or myself, I always want more answers, and I always want to help others understand. The best way to get a patient to comply with treatment is to have them, at some level, understand *WHY* you are suggesting the treatment. As my career moved forward, I was drawn to what was poorly understood. Two areas caught my interest and compelled my research. Why did patients with obsessive-compulsive disorder (OCD), despite their insight into the irrational nature of this obsession, continue to do their compulsions to relieve their anxiety? Moreover, what was the role of genetics in serious mental illnesses? I doubted that genetics would explain everything, but clearly, many of these disorders are familial.

Figure 1. Michele Pato, MD, Rutgers University, USA.

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

Too many things come to mind, but watching the lunar module land and humans walk on the moon is definitely one of them. My Dad worked for Grumman aircraft at the time and helped design the air conditioning and heating of the Lunar module.

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

To help people feel better and reduce their suffering.

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

Nature and nurture are both important to living the fullest, most enjoyable life. It is never just about our genes but what you do with them and what you bring to the table. As I analyze our data, write papers, and work on presentations, I always ask if it makes sense, if I have the correct hypothesis, and if there is a better way to explain it.

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What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
In many settings I felt encouraged to pose a question if something was not clear to me. I ensure that those working with me feel that it is fine to admit if they are not following along and to seek a clearer explanation.

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?
Supporting the careers of women in science. Women are great scientists. And even unique because they bring a different perspective to answering questions.

What do you most enjoy in your capacity as an academic or research leader?
Encouraging every physician to be a scientist. Never simply do something because that is the way it has always been done. Never be afraid to ask questions, especially when something does not go the way you expect: sometimes the unexpected teaches you the most!

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?
I love to cook. I so enjoy sharing my creativity in this way with others. I am basically a very social person and love spending time with friends and family in the kitchen. Food is a great vehicle for communication.

Part 2: Michele Pato – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Sharing thoughts and time with friends who let you be yourself and value your thoughts.

What is your greatest fear?
Not employing the skills I have been given to do the most good.

Which living person do you most admire?
This is a hard one for me to answer. People, of all backgrounds, have influenced me in so many different spheres of my life, and it is hard to pick just one. Overall, I have always admired the positive contributions.

What is your greatest extravagance?
A restaurant grade kitchen and all the pieces that go with it.

What are you most proud of?
Inspiring others to do research in medicine and to help others.

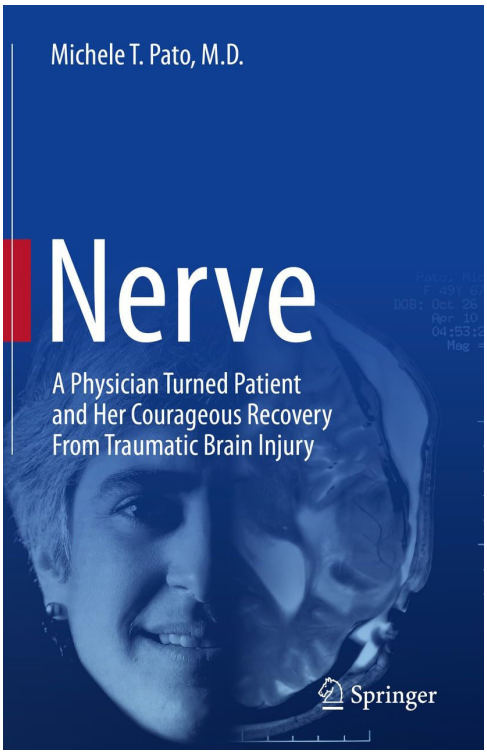

Figure 2. Michele Pato's book *NERVE*, on recovery from traumatic brain injury.

What is your greatest regret?
I never focus on what I have accomplished but constantly think about what still needs to be done. It is essential to take the time to celebrate your successes.

What is the quality you most admire in people?
Forgiveness. Being able to see beyond another's weaknesses or meanness and instead see their strengths and kindness.

What do you consider the most overrated virtue?
IQ without sensitivity.

What is your favorite activity (physical or intellectual)?
Cooking and baking.

Where would you most like to live?
With my husband and near my family and friends. Home is wherever they are with me.

What is your most treasured possession?
My "brain/mind." I am a Traumatic Brain Injury survivor. Eighteen years ago, I was hit by a car, and my head was wedged in a wrought iron fence. Half my skull was removed for a month and put on ice so my brain could expand without being crushed. No one knew how much I would recover. I had no choice but to use my brain (and mind) to get better. And I did. I wrote about my first 15 years of recovery in a memoir recently published by Springer titled *NERVE* (figure 2).

When and where were you happiest?
Now. Take every moment for what it gives and what you can give it.

What is your most marked characteristic?
It is my expressiveness. I talk not just with my voice but with my hands and body.

[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. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, 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.

Among your talents, which one do you think gives you a competitive edge?
Not being afraid to ask questions. I always like to say there is no such thing as a dumb question; the only dumb thing is not asking one. Not asking questions means you do not know what you do not know, which can be dangerous.

What is a personality/characteristic trait you wish you had?
More confidence that people value me for who I am.

What do you consider your greatest achievement?
Helping others. Writing the book *NERVE* was about giving people hope and helping them develop resilience. Using your strengths to cope with weaknesses, and we all have weaknesses.

What do you most value in your friends?
A sympathetic ear. A willingness to listen.

Who are your favorite writers?
RD Robb, Yotam Ottolenghi, Jamie Oliver, Olivier Sacks, and Malcolm Gladwell.

Who are your heroes of fiction?
It depends on what I need to inspire me at the time, and then I read fiction.

Who are your heroes in real life?
I do not have a single hero. I love to collect quotes and use the wisdom of others in the moment to remind me to value what I am experiencing.

What aphorism or motto best encapsulates your life philosophy?
I have two: "Never give up." "Life is not measured by the number of breaths you take but by the moments that take your breath away."

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INNOVATORS & IDEAS: RESEARCH LEADER

Peter W. Kalivas: To the tetrapartite synapse and beyond – A pathway for new drug targets to treat behavioral disorders

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Keywords: Synapse, astroglia, extracellular matrix, microglia, stress, substance use

Peter Kalivas stands as a pioneering architect in our understanding of addiction neuroscience, having transformed our knowledge of how substances of abuse reshape brain circuits and cellular function. Over four decades, his groundbreaking research has illuminated the fundamental mechanisms underlying substance use disorders, mainly through his seminal discoveries of glutamate's critical role in addiction and his innovative work on the "tetrapartite synapse" – revealing how astroglia and the extracellular matrix regulate addictive behaviors. With over 400 publications and eight edited volumes, his research has revolutionized our conceptual framework for treating addiction by identifying novel therapeutic targets beyond traditional neurotransmitter systems. After receiving his PhD in Pharmacology from the University of Washington and completing postdoctoral training at the University of North Carolina, Dr. Kalivas built an extraordinary scientific legacy at Washington State University and then as the founding Chair of Neuroscience at the Medical University of South Carolina. There, he established a world-renowned research program that has trained generations of addiction scientists while developing innovative approaches to understanding stress, PTSD, and substance use disorders. Now serving as Distinguished University Professor, he continues to pioneer new frontiers in addiction neuroscience through his work on neural circuits and synaptic plasticity. In this Genomic Press Interview, Dr. Kalivas shares insights from his remarkable journey investigating the neurobiology of addiction and his vision for the field's future.

Part 1: Peter W. Kalivas – Life and Career

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

My Dad was a physician in private practice who brought home a microscope and histology from various tissues for me in the 4th grade. I was already interested in science, but this kindled my interest in biology. The other big influence was the Golden Book Encyclopedia I avidly read cover to cover in grammar school as each issue came out.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

Leadership was not my goal, at least not consciously. That said, as a professor at Washington State University's School of Veterinary Medicine, I was isolated and falling behind my colleagues at institutions with a larger critical mass in researching substance use disorder. In the late 1990s, I looked at endowed chair positions and decided to interview in Charleston for an open Chair of Physiology. Growing up in Los Angeles, I found the idea of being on the coast in a warm place appealing but running a department was not so appealing. However, Charleston came together with an excellent start-up opportunity to build a Department of Neuroscience where I could create a critical mass of research faculty. Equally important, Sue (my wife) and I agreed that it would be a great place to live and finish raising our kids. We were on a 10-year plan that is now in its 25th year.

Figure 1. Peter Kalivas, PhD, Medical University of South Carolina, USA.

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

I was initially focused on environmental science as a college sophomore, but after reading the Ghost in the Machine by Arthur Koestler who introduced me to Robert MacClean's ideas of schizophysiology I became interested in how the brain functions. About the same time I did a term paper on the work by Conrad Waddington who first coined the term epigenetics as a way to bridge Darwin and Lamarck. Together, these moved me towards a career in neuroscience.

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What impact do you hope to achieve in your field by focusing on specific research topics?
My hopes have changed over my career from grandiose early on to more practical as time went by. Initially (as an undergraduate), I wanted to figure out mechanistically how the brain creates emotions, spiritual feelings, and thoughts. This tilted towards less grandiose goals related to how psychotropic drugs affect the brain as I came to personally experiment with various mind-altering substances. As with most of us in the early days of neuroscience, I gradually settled on more practical goals, such as understanding how the cortex regulates the nucleus accumbens in order to help understand disorders such as substance use. Of course, while that hope led to many discoveries, translating even those simpler goals into treatments proved elusive for my entire career. Nonetheless, hope springs eternal. I believe in the human capacity to discover and create, and I am grateful to have played a small role in helping us eventually achieve some of my earlier aspirations.

Please tell us more about your current scholarly focal points within your chosen field of science.
As implied in the previous answer, my research goals and discoveries became more reductionist over time due to a need to find concrete answers to questions, believing that this could lead to interventions in psychiatric disorders. On this trajectory, I have gone in two general directions, improving preclinical behavioral models of substance use disorder and understanding how the neuropil in which synapses are embedded is essential in curating synaptic activity. In the former, we have explored algorithms for nonlinear modeling of multiple addiction-like behaviors in outbred rats to mimic humans' genetic variability more accurately. By taking multiple traits together and clustering them into resilient and vulnerable subpopulations, we are isolating genetic and transcriptomic traits that may contribute to substance use disorders (SUDs) in humans. For the latter, we are in the vanguard of understanding the 'tetrapartite synapse' – examining how astroglia and extracellular matrix influence synaptic connections between neurons, particularly in pathways from the cortex to nucleus accumbens that regulate reward and addiction-like behaviors. By including key cellular components of the neuropil that in how addictive drugs induce synaptic plasticity, we have encountered new potential molecular mechanisms that in rodents can countermand cue-induced drug seeking.

Early on we focused on a discovery that dysregulation of the astroglial cystine/glutamate exchanger was produced by cocaine use and that restoring it with N-acetylcysteine reduced cued seeking. This was moved into clinical trials with success in reducing cued-craving and in some studies reducing drug use, but it was ineffective in a broad population of significantly reducing relapse except in certain subpopulations, such as already abstinent cocaine users and adolescent cannabis users. The apparent positive effects in subpopulations was an impetus for exploring novel ways to identify subpopulations of rodents using heroin (as mentioned above). Also, this discovery in a possible role for an astroglial protein in regulating drug-relapse induced synaptic plasticity led to two decades of research into how both astroglia and the extracellular matrix regulate both natural reward and drug-induced plasticity in the nucleus accumbens (as also mentioned above).

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
The most critical habit is the ability to focus for hours on end on experimentation and writing. The most important value is that scientific research is a personal art form, akin to painting or any other endeavor where the thrill of discovery and exploration energizes you. With this in mind, in pursuing a career as an experimentalist, I found the hierarchy within science was largely irrelevant to discovery; rather, it was more important to be embedded in a team of colleagues from technicians to students to Principal Investigators (PIs) who have varied perspectives that could shape our research. Of course, the community of science is relevant for funding research, obtaining notoriety in the field, and finding great colleagues and friends.

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?
First, I was often so wrapped up in conducting competitive research and publishing that only in the last 15 years or so did I come to fully appreciate how grateful I am for the opportunities I was afforded, primarily by taxpayers who are incredibly generous in funding most of my research. The non-science taxpayers need to be admired for their generosity and belief in the positive force scientific discovery brings to civilization. They should be brought into the discussion of science as essential partners. More to the point of the question. Being raised in an upper-middle-class family but attending a public school system that was socio-economically diverse gave me a combination of early exposure to science as well as an appreciation for the role that people with different backgrounds play in advancing human civilization. I applaud the efforts by most of the scientific community to broaden our workforce to include people from all types of backgrounds.

What do you most enjoy in your capacity as an academic or research leader?
I have always enjoyed the sense of optimism and excitement of making discoveries in the lab the most. This is amplified by working with my labmates on the same discoveries. As a department chair, this was further amplified by having the resources to play a small role in helping young faculty build their research careers.

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?
I spend my leisure exploring the world around me. This takes many forms, from walking in the woods to flying around the world and experiencing cultures and ecosystems that are new to me.

Part 2: Peter W. Kalivas – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
I am not a big fan of perfection, which I see as a false goal. That said, happiness comes in many forms and really amounts to a general state of optimism, relationships and personal exploration. Family and friends are key facilitators of this state of mind for me.

What is your greatest fear?
It is cliché, but I believe that "the only thing we have to fear is fear itself" (Franklin D. Roosevelt's First Inaugural Address, 1933). More specifically, in my lifetime, I have watched fear sap energy from things as varied as the space program to social cohesion. I fear that a political culture using fear

[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. Scientific discovery, like life, is a personal art form. Have fun!

as a means to power is detrimental to the scientific and cultural development of our civilization to culturally and scientifically evolve in response to an ever-changing world.

Which living person do you most admire?
The more I can share and empathize with another person, the more I admire them. To follow this to its logical conclusion, I would say my wife, Sue King who spent her career as a social worker with children.

What is your greatest extravagance?
Indulging my passion for travel by flying.

What are you most proud of?
It is prosaic but true to say: my children. This is followed by how well most of the people passing through my lab and department have done for themselves both in their career and personal lives.

What is your greatest regret?
I regret not living to be 500 years old, so I would have time to experience different walks of life.

What is the quality you most admire in people?
Kindness and trust, which are the antithesis of fear.

What is the trait you most dislike in people?
Materialism as a substitute for personal growth.

What do you consider the most overrated virtue?
Believing in absolute truth, which distorts understanding the ever-changing reality we live with.

What is your favorite occupation (or activity)?
Experiencing new things.

Where would you most like to live?
Southern California, with 10% as many people.

What is your most treasured possession?
My physical and mental health.

When and where were you happiest? And why were so happy then?
It is tough to rank-order something like happiness. As I said above, happiness is a state of mind not necessarily linked to a specific event. It is best experienced and shared with others but arises internally sometimes when least expected. It is easier to say in concrete terms what makes me unhappy.

What is your current state of mind?
Relatively at peace, trying to answer questions that go beyond words.

What is your most marked characteristic?
I like to think it is tolerance, that comes from trying to accept the world as it is, not necessarily how I think it should be. This came in handy as a scientist whose hypotheses were often proven only partly correct or wrong upon further experimentation.

Among your talents, which one(s) give(s) you a competitive edge?
Intense focus of attention and generally not taking things personally.

What do you consider your greatest achievement?
I will answer this in terms of my career. I hope the people who passed through my lab learned as much from me as I did from them. When I step aside, they will be the ones left to explore and make important, novel discoveries.

If you could change one thing about yourself, what would it be?
To have been less afraid of what others think of me, especially when I was younger. It created a lot of unnecessary anxiety and got in my way, especially during public speaking. I self-medicated with beta blockers to treat public speaking anxiety for the first 10–15 years of my career.

What do you most value in your friends?
Kindness and an ability to surprise.

Who are your favorite writers?
Richard Powers for his descriptions of biological ecosystems that put words to things I experienced but had no words. I also enjoyed Ayn Rand, both for the empowering portrayal of what ambitious, committed people can accomplish, but also for revealing that ambition at the expense of others is an important guardrail to be aware of in building a successful career.

Who are your heroes of fiction?
Reading fiction for me until now has been mostly a way to relax and escape, so I never really found a hero. That said, a person (rather mutant) that comes to mind is Charles Francis Xavier, better known as Professor X, has been guiding the X-Men since his first appearance in Marvel Comics' The X-Men #1 in September 1963. The brainchild of Stan Lee and Jack Kirby, Professor X serves humanity with intelligence and humility, not a bad role model.

Who are your heroes in real life?
I admire most people who have had a large personal career and, in later life, give back out of gratitude for what they have received. Jimmy Carter comes to mind.

What aphorism or motto best encapsulates your life philosophy?
Fortune favors the brave.[2]

Charleston, South Carolina, USA
25 November 2024

Peter W. Kalivas[1]
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[2] "Fortune favors the brave" traces back to ancient Rome, first appearing in Virgil's Aeneid as "audentes Fortuna iuvat" (29-19 BCE) and in Terence's Phormio (161 BCE) as "Fortes fortuna adiuvat." The saying spread across Europe over centuries and lives on today as a motto for military units like the U.S. 3rd Marine Regiment. While often credited to Pliny the Elder, scholars cannot confirm he actually coined the famous version we use today – it seems to have evolved naturally from these earlier Roman sources over time.

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INNOVATORS & IDEAS: RESEARCH LEADER

Carmine Maria Pariante: Understanding why and how stress makes us ill

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Keywords: stress, depression, inflammation, creativity, mental health, public engagement

Carmine M. Pariante is Professor of Biological Psychiatry at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, and Consultant Perinatal Psychiatrist at the South London and Maudsley NHS Foundation Trust. He investigates the role of stress and inflammation in the pathogenesis of mental disorders and in the response to psychotropic drugs, both in clinical and experimental settings. His work focuses on depression and fatigue, with a particular interest in the perinatal period and individuals with medical disorders. More recently, he has developed an interest in the effects of the arts, social prescribing, and nutritional interventions on mental health. Since 2018, Professor Pariante has been a Clarivate Analytics Highly Cited Researcher, and, as of April 2024, he has published >520 publications, with close to 40,000 citations and an H-Index of 103 in Scopus and 137 in Google Scholar. He is also the appointed Editor in Chief of the journal *Brain Behaviour and Immunity* and the Past President of the International Society for Psychoneuroendocrinology. Professor Pariante is also passionate about public engagement and has made many media appearances in newspapers, magazines, radio, and TV on topics broadly related to mental health, writing pieces for the *Daily Mail*, *The Guardian*, and the *New Humanist*. He can be followed on X and Instagram on @Pariantelab and the digital publication he edits, www.inspirethemind.org. It is gratifying to see Professor Pariante share insights into his professional and personal voyage during the Genomic Press interview.

Figure 1. Carmine M. Pariante, MD, PhD, King's College London, UK.

Part 1: Carmine M. Pariante – 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 have always wanted to be a psychiatrist. My parents were both psychiatrists, and I read Freud when I was in school. I was captivated by the psychoanalytical themes in Hitchcock's movies. Then, in my first year of medical school, I was gobsmacked by the complexity of the brain. This was the perfect recipe, or perhaps the perfect storm, to drive my passion for research in the biology of mental health.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channelled you toward that leadership responsibility?

I have had a very linear career path. I spent the first 28 years of my life in my country, Italy, where I attended medical school in Rome (1990) and part of my psychiatry training in Cagliari (1994). Then, in January 1995, I left Italy for the US – and I have never had a job in Italy since then. In the US, I was a Research Fellow in Psychiatry at Emory University in Atlanta, working with Andrew H. Miller and Charles B. Nemeroff, who have remained to date my close friends and mentors. In 1997, I moved to London to the (then) Institute of Psychiatry, and I progressed here throughout my clinical academic career until becoming a Full Professor in 2012. My institution has changed its name (it is now called Institute of Psychiatry, Psychology and Neuroscience at King's College London), but I have never moved, mostly because I have found here so many friends and colleagues, such as Robin Murray and Simon Wessely – as well as a fantastic team of junior researchers that have always been a dream to work with, and who have progressed over the years to become independent, established academics. Of the many leadership roles I have had over the years – as editor of scientific journals, president of societies, and leader of research programs – nothing gives me the same joy, fire, and challenge as leading my amazing research team.

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

My MD research project in 1990, and the resulting first publication in 1991, was on depression and the immune system. I do not know why I fell in love with "psycho-neuro-immune-endocrinology," an area that at that time was quite a niche and had not yet entered mainstream psychiatry and neuroscience research. The notion of such a profound and reciprocal communication between the brain and the body resonated at that time with my holistic view of the human being and my understanding of mental health as interlinked with physical health. At the same time, the deep molecular and cellular dimensions of psycho-neuro-immune-endocrinology triggered the curiosity of the basic scientist in me. I have remained loyal to this initial passion until today.

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

I have one ambition and one ambition only: to tap into psycho-neuro-immune-endocrinological mechanisms in order to develop new medications and treatment strategies for people with mental health problems that are not responding to currently available medications. Moreover, there are plenty of people like this.

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Figure 2. Carmine Pariante after a run in Villa Borghese, Rome; in the background, Piazza del Popolo and San Pietro.

Please tell us more about your current scholarly focal points within your chosen field of science.
Focus is not, unfortunately, my main strength! In terms of psycho-neuro-immune-endocrinology, we have just started an international research programme called ASPIRE, funded by Wellcome, to understand the best predictors to identify depressed people who will respond to anti-inflammatory medications. In parallel, I am continuing my research in perinatal mental health, and in depression in pregnancy in particular, through a European programme called HappyMums, of which I lead the clinical component. I know that improving maternal mental health will prevent mental health problems in the next generations. Finally, I am in the exciting final phase of SHAPER, a Wellcome-funded research programme testing arts interventions in mental health, including post-natal depression, and papers from these studies should come out soon.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
Work hard, and have lots of fun. I know it is a bit of a cliché, but I firmly believe that the harsh life of research and academia cannot be sustained only by high-impact papers and prestigious grants. We need to feel comfortable letting our hair down with our friends, colleagues, and co-workers, and I strive to make sure that my research team is famous not only for the great work we deliver but also for the great fun we bring to conferences' parties.

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?
My perspective on diversity and inclusion has been shaped by both the privilege of being a white man and the difficulties of being an immigrant. I have always supported young researchers from all backgrounds, regardless of their personal and demographic traits, and I am profoundly disturbed when I see bullying or discriminatory behaviour.

What do you most enjoy in your capacity as an academic or research leader?
Seeing my team's researchers pushing beyond their limits and reaching successes that they thought would have never been possible.

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?
I have many passions—as I have said, focus is not my forte. I am a senior student of kung fu, which gives me physical, mental, and spiritual strength. I am also passionate about physical activity, including running, cross-training, and obstacle races. As soon as I can, I jump on a plane to a remote destination where it is very hot, there is a sea, and I can't understand a word of what people or street signs are saying.

Part 2: Carmine M. Pariante – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Sipping a cold beer and watching life go by in the aforementioned remote, hot, sea-facing place.

What is your greatest fear?
Not to be loved.

Which living person do you most admire?
Margaret Atwood. She is a great writer and a courageous defendant of democracy, equality, and freedom.

What is your greatest extravagance?
I love the San Remo music festival, Eurovision, trash music, and TV.

What are you most proud of?
Having run five Tough Mudder races in 5 years.

What is your greatest regret?
I should have taken a gap year when I was young. Nevertheless, there is still time.

What is the quality you most admire in people?
The ability to inspire other people. I listen to politicians, writers, and intellectuals, or I read their prose, and I think – wow, I wish I could have said that.

What is the trait you most dislike in people?
Arrogance and self-entitlement.

What do you consider the most overrated virtue?
Working hard, when it is the only thing one does.

[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.

What is your favourite occupation (or activity)?
When I am not training as a martial artist, and weather permitting, I love to hike and scuba-dive.

Where would you most like to live?
In a small island in a small house with a small terrace overlooking the sea.

What is your most treasured possession?
Photos from my childhood and youth.

When and where were you happiest? And why were you so happy then?
Today is always the happiest day of my life. Not only have I been alive for one more day, but I have also learnt something new that will make tomorrow even better.

What is your current state of mind?
As I am writing this in April 2024, I am still affected by the loss of both my parents less than six months ago. I am grateful because I have an incredible support network at home and work; slowly, I am returning to normal.

What is your most marked characteristic?
I am loyal. I am a loyal friend and colleague and fearlessly protective of my team.

Among your talents, which one(s) give(s) you a competitive edge?
I am diplomatic, a great negotiator, and can bring people together.

What do you consider your greatest achievement?
Together with my team, I have created from scratch a new mental health digital magazine called Inspire the Mind (www.inspirethemind.org). In 5 years, it has gone from a laboratory blog to an internationally renowned, award-winning platform for public dissemination in mental health, with more than 250K views.

If you could change one thing about yourself, what would it be?
I want to stop doubting myself so frequently.

What do you most value in your friends?
Being able to count on them.

Who are your favourite writers?
Jonathan Franzen, Haruki Murakami, Kazuo Ishiguro, Javier Marías

Who are your heroes of fiction?
The man with no name in Sergio Leone's Western movies

Who are your heroes in real life?
Teachers, doctors, nurses, social workers – everybody who works hard for the community.

What aphorism or motto best encapsulates your life philosophy?
There is always a way.

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INNOVATORS & IDEAS: RESEARCH LEADER

Paola Dazzan: What can we do to understand psychosis?

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Keywords: Neuroimaging, psychosis, neurobiology, outcome, first episode, postpartum psychosis

Professor Paola Dazzan is a prominent researcher who currently holds the positions of Professor of Neurobiology of Psychosis and Vice Dean for International Affairs at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK. She practices as a Consultant Perinatal Psychiatrist at the South London and Maudsley NHS Foundation Trust. Originally from Italy, Professor Dazzan began her academic journey by attending Medical School and becoming a practicing physician. Following her graduation, she continued with her training as a psychiatrist at the Maudsley Hospital and is a Fellow of the Royal College of Psychiatrists. She completed her PhD at the Institute of Psychiatry, Psychology and Neuroscience King's College London, and has worked there ever since. She is internationally known for her work using brain magnetic resonance imaging (MRI) data, stress and inflammatory markers, and reproductive hormones, to understand the onset and outcome of psychoses and of other severe psychiatric disorders. Her contributions have been widely recognized in the international psychiatric community and she is recognized as a leading researcher in the field. We are delighted that Professor Paola Dazzan has kindly agreed to participate in the Genomic Press Interview. We hope that our readers will discover many intriguing facts about her personality, work, and innovative research.

Part 1: Paola Dazzan – 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 born In Italy, and while attending high school, I became familiar with the work of Freud and Jung, which was part of our philosophy curriculum. This triggered my interest in the mind, how our personal experiences shape our behaviour and our view of the world, and how we could intervene to make people feel better. From here, I decided I wanted to become a psychiatrist and attended Medical School with this objective. I was very fortunate to make this dream a reality and have never regretted my choice.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channelled you toward that leadership responsibility?

After completing Medical School in 1994, I had the opportunity to spend a period of time at what was at the time the Institute of Psychiatry in London (UK), thanks to a fellowship. My time at the Institute was life-changing, as I was suddenly exposed to an environment where education and research went hand in hand, taught by the big names in psychiatry. I felt like I found my home, and I decided to stay after my fellowship ended. So, what was supposed to be a 10-month experience has become the last 30 years of my life! In 1996, I joined the Maudsley training program to become a specialist, and then in 2006, I completed my PhD under the supervision of Robin Murray. My whole career has been spent in this Institution, where I met many supportive peers who trusted me in taking on more and more senior leadership positions. After I became a full Professor in 2016, I took on leadership roles in two areas I am passionate about: diversity and inclusion and international partnerships.

Figure 1. Paola Dazzan, MD, PhD, King's College London, UK.

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

Being at the Maudsley and the Institute of Psychiatry during my training was like being in a "shopping centre" of psychiatry. Every subspecialty or area of research was suddenly available to study. It was during this time that psychosis caught my interest out of a desire to understand more about how our brain can give origin to such unusual and often distressing experiences. I discussed my interest with Robin Murray, who was always open to discussing research with us trainees, and, following his advice, I spent six months at Johns Hopkins University, in Godfrey Pearlson's laboratory, learning neuroimaging. On my return, I found waiting for me the incredible opportunity to start my PhD with Robin, using neuroimaging in the AESOP study of first-episode psychosis.

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

My area of research is centred on the identification of clinical and neurobiological predictors of treatment response in psychosis. Unfortunately, in the last twenty years, the search for neuroimaging or blood-based

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Figure 2. Paola Dazzan in the Seychelles, enjoying herself at one of the world's most beautiful, wild beaches.

biomarkers predicting treatment response and outcome of psychosis has not yet been as successful as we had hoped. Still, I think even these failures have brought us new awareness of the complex heterogeneity of the disorders we are studying and pushed us toward the application of new, different approaches to studying the neurobiology of psychosis. My research will contribute to identifying more effective ways to stratify individuals in treatment trials so that interventions can be as tailored in psychiatry as in other branches of medicine.

Please tell us more about your current scholarly focal points within your chosen field of science.
At present, I am completing the three-year *eBRAIN* study, a large longitudinal study of young adolescents to explore the impact of early adversity on trajectories of brain development and the onset of psychotic experiences and poor mental health in general, also looking at the potential mediating role of the immune system. I am also working with young people to co-develop a framework of guidelines for conducting biological research in mental health in the *CELEBRATE* project. These guidelines will help researchers to recruit and retain representative cohorts of young people in biological studies, using, for example, neuroimaging or collections of blood samples.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
The principal value that I uphold is respect. I grew up with parents who were always respectful, even when imparting discipline, and growing up, I have expected this from others. As such, I ensure I also respect people, their opinions, and their diversity, independently of their roles, and promote this within my research group. There is always a way to be sensitive and thoughtful when communicating, even in disagreement. Living in a multicultural environment like London has also made me value the power that different backgrounds and perspectives can bring to a common objective and academic and non-academic life in general.

At Genomic Press, we prioritize fostering research endeavours 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?
Although some progress has been made, we must still achieve equality and inclusivity in science. We still need to scrutinize our attitude to gender or underrepresented groups. This remains a massive problem in academia, and science must acknowledge and address these biases. As a woman, I have experienced many of the negative attitudes, whether conscious or unconscious, that can hamper progression for some individuals. We all need to fight these, as you are doing with Genomic Press.

What do you most enjoy in your capacity as an academic or research leader?
Working with young people who have the energy to bring new ideas and new perspectives to old problems.

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?
I love travelling, so when I am not working, I usually explore or plan to explore other countries. When in London, I run, do yoga, or meet friends in my free time.

Part 2: Paola Dazzan – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Relaxing on a beautiful beach (see figure 2) with the people I love next to me.

What is your greatest fear?
Losing my mobility.

[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.

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Which living person do you most admire?
Nobel Laureate Denis Mukwege, a gynaecologist who has treated thousands of survivors of sexual violence by armed groups, and who fights to have rape recognized as a weapon of war.

What is your greatest extravagance?
Wearing big, chunky, and cheap costume jewellery.

What are you most proud of?
The support I give to those who need it, whether family, friends, or those working with me.

What is your greatest regret?
Not having done a gap year after university. I am now counting on doing a Senior gap year!

What is the quality you most admire in people?
Honesty.

What is the trait you most dislike in people?
The inability to listen to others.

What do you consider the most overrated virtue?
Extroversion (is it a virtue, though?)

What is your favourite occupation (or activity)?
Reading, preferably while lying on a beach.

Where would you most like to live?
South-East Asia.

What is your most treasured possession?
The gift of unconditional love given by my parents.

When and where were you happiest? And why were so happy then?
I have always been happiest when travelling. I get thrilled by exploring new places and meeting people living in a different environment. While there, I enjoy hiking, diving, or just watching life go by while sitting in a café for a whole afternoon.

What is your current state of mind?
I am happy and satisfied, as one of my PhD students just passed her viva with lots of compliments from the examiners! We will all celebrate her in a couple of hours.

What is your most marked characteristic?
Discretion.

Among your talents, which one(s) give(s) you a competitive edge?
Being an independent thinker.

What do you consider your greatest achievement?
Having had some young colleagues telling me I have been a role model for them.

If you could change one thing about yourself, what would it be?
The fact that my face reflects so openly what I am thinking.

What do you most value in your friends?
Loyalty.

Who are your favourite writers?
Gabriel Garcia Marquez, Margaret Atwood, Jonathan Franzen, Bernardine Evaristo.

Who are your heroes of fiction?
Nancy Drew. As a young teenager, I loved her books, admired how smart and independent she was, and dreamt of becoming like her!

Who are your heroes in real life?
Those who speak up to defend a just cause, even knowing that they are putting their lives in danger.

What aphorism or motto best encapsulates your life philosophy?
What you do not want done to yourself, do not do to others.

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INNOVATORS & IDEAS: RESEARCH LEADER

Keqiang Ye: The C/EBPb/AEP pathway is the key driver for Alzheimer's disease (AD) and Parkinson's disease (PD) pathogenesis and its specific inhibitor attenuates AD/PD pathologies

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Keywords: α-Synuclein, Alzheimer's disease, Asparagine Endopeptidase (AEP), CCAAT/Enhancer Binding Protein Beta (C/EBPβ), Parkinson's disease, positron emission tomography tracer.

Dr. Keqiang Ye is currently an endowed professor and Department of Biology Chairman at Shenzhen Institute of Advanced Technology (SIAT), China. Prior to this role, he held positions at Emory University in Atlanta, Georgia, USA, serving as an Assistant Professor (2001–2007), a tenured Associate Professor (2007–2010), and a Full Professor (2010–2021). He has received numerous professional honors, notably the Distinguished Scientist Award from the Sontag Foundation (2003) and the American Cancer Research Scholar Award (2004). His research focuses on neurodegenerative diseases, including molecular mechanisms in pathogenesis, early diagnosis, and drug development. With 265 published papers, including contributions to esteemed journals such as *Cell*, *Nature*, *Nature Medicine*, *Neuron*, and *PNAS*, among others, Dr. Ye has made significant strides in identifying novel compounds with therapeutic potential for treating neurological diseases, particularly Alzheimer's disease (AD). His work has led to the licensing of these drugs by pharmaceutical companies and their ongoing clinical development. Dr. Ye shares with our readers the highlights of his professional and personal journeys.

The Genomic Press Interview Part 1: Keqiang Ye – Life and Career

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

As a rotation graduate student at Emory, I discovered noscapine, a natural product, as an anticancer drug through a visual structural comparison of known microtubule inhibitors from the Sigma catalog. This discovery led to the publication of my first *PNAS* paper as part of my PhD thesis, and noscapine was licensed by a biotech company and progressed into clinical trials against prostate cancer. As a postdoc at Johns Hopkins University, I furthered my research by uncovering the role of PIKE GTPase in mediating nuclear PI3K signaling (*Cell*, 2000), PLC-γ1's mitogenic effect via nerve growth factor (NGF)-triggered PLC-γ1 nuclear translocation and PIKE activation (*Nature*, 2002 and featured as a research highlight by *Nature Reviews Molecular Cell Biology*, 2002;3:149). These exciting findings not only advanced scientific knowledge but also fueled my enduring passion for science and drug discovery.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

As a faculty member at Emory, my lab dissected how neurotrophin-provoked nuclear PIKE/PI3K signaling promotes neuronal survival and published dozens of top-level papers (*Nature Neuroscience*, 2003; *Molecular Cell*, 2005; *EMBO Journal*, 2004, 2006; *Nature Cell Biology*, 2007, 2008). As a faculty member at Emory, my belief in dedicated work and a problem-solving approach has been crucial in shaping my leadership journey. I have always endeavored to maintain a holistic view of our research efforts, ensuring that I provide instructive guidance and support to students. Meanwhile, I work closely with my team, fostering a collaborative environment and guiding them through challenges. Over 20 years, positive feedback and notable achievements have further bolstered my faith in this approach. The identification of the small molecular TrkB agonist, 7,8-DHF, and its translational impact, including the FDA approval for R13 (a prodrug of 7,8-DHF) IND for Alzheimer's disease (AD) indication and the initiation of phase I clinical trials have supported our methods and leadership style.

Figure 1. Keqiang Ye, PhD, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, China.

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

My lab discovered that AEP, an acidosis-activated protease, cuts SET, which is a DNase inhibitor during stroke, which can be antagonized by

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PIKE (*Molecular Cell*, 2008). This finding was made by serendipity due to preparing the buffer at wrong pH values. My team disclosed that AEP, an asparagine endopeptidase, acts as a delta-secretase that cleaves APP, Tau, and α-Synuclein, promoting AD and Parkinson's disease (PD) pathogenesis.

What kind of impact do you hope to achieve in your field through your focus on your specific research topics?
Based on dozens of top-tier publications, I have put forward a conceptually novel theory that the C/EBPβ/AEP pathway is the key driver for AD/PD pathogenesis and its specific inhibitor attenuates pathologies and restores cognitive or motor functions.

Could you tell us about your current scholarly focal points within your chosen field of science?
On the basis of this theory, our team has found that follicle-stimulating hormone (FSH), which drastically escalates after menopause, not only drives osteoporosis but also activates the aforementioned signaling pathway, preferentially instigating AD onset in women (*Nature*, 2022). This discovery sheds light on the perpetual puzzle of why women are more vulnerable to AD onset. Moreover, our team has successfully identified a long-awaited α-Synuclein PET tracer, F0502B, for PD diagnosis (*Cell*, 2023).

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences, that you uphold within your own research environment?
Proposing a hypothesis based on the principles of natural philosophy and addressing a question starting from the epidemiology and unbiased global findings or big datasets are the main habits!

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 you think warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?
To discover the master regulator driving the aging process that not only dictates the lifespan but also encodes different age-dependent diseases' onset and progression deeply stirs my scientific passion.

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?
Reading books about history, war, philosophy, fishing, or playing Texas Hold'em POKER are the most preferred leisure moments.

The Genomic Press Interview Part 2: Keqiang Ye – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Perfect happiness would be the pleasure arising from internal spiritual peace.

What is your greatest fear?
Dismal worrisome uncertainty.

Which living person do you most admire?
My postdoc mentor Dr. Solomon H. Snyder.

What is your greatest extravagance?
To enjoy leisure during the working day.

What are you most proud of?
To single out the key dominant feature from a gigantic tangled dynamic mess!

What is your greatest regret?
We have yet to be able to dissect the reproducible technical experimental details for TrkB receptor activation in primary neurons by its small molecular agonist.

What is the quality you most admire in people?
Dauntless courage and imagination.

What do you consider the most overrated virtue?
The relentless pursuit of perfection.

What is your favorite activity (physical or intellectual)?
Fishing!

Where would you most like to live?
Southern California or Shenzhen, China.

What is your most treasured possession?
Inherent ambition.

When and where were you the happiest? And why were you so happy then?
The first year (1993) when I came to Emory University (Atlanta, Georgia, USA) as a graduate student from China has been the happiest moment in my life. The lifestyle change was drastic and everything around me is so amazing!

What is your most marked characteristic?
Perseverance.

Among your talents, which one do you think gives you a competitive edge?
Imagination.

What is a personality/characteristic trait you wish you had?
Tolerance/patience.

What do you consider your greatest achievement?
To establish the theory that C/EBPb/AEP signaling is the single key driver for aging and age-related disorders.

What do you most value in your friends?
Honesty.

Who are your favorite writers?
Victor Hugo and Mao Zedong.

Who are your heroes of fiction?
The Monkey King.

Who are your heroes in real life?
Albert Einstein and Solomon H. Snyder.

[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. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, 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.

What aphorism or motto best encapsulates your life philosophy?
Money takes care of itself!

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Brain Medicine

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COMMENTARY

Human microplastic removal: what does the evidence tell us?

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Keywords: Microplastic, environment, brain, dementia, health, removal

The increased levels of microplastics and nanoplastics (MNPs) found in human brain tissue are alarming, particularly in patients with dementia. Although total avoidance of MNP exposure will likely remain an unattainable endpoint in light of their ubiquity in the environment, new studies indicate feasible pathways by which dietary intake may be decreased or clearances improved. This commentary reviews the evidence on human exposure to MNPs, their tissue penetration, and potential health effects, particularly on neurotoxicity. We will explore evidence-based strategies for reducing exposure through dietary and lifestyle changes while addressing key gaps in our current knowledge calling for additional research.

A recent paper in *Nature Medicine* by Nihart et al. found that the human brain contains approximately a spoon's worth of microplastics and nanoplastics (MNPs), with levels 3–5 times higher in those with a cohort of decedent brains with a documented dementia diagnosis (with notable deposition in cerebrovascular walls and immune cells) (1). Particularly, brain tissues were found to have 7–30 times higher amounts of MNPs than other organs such as the liver or kidney. Also of note, the microplastics in the brain were of a smaller size (<200 nm) and most often polyethylene. Although MNP concentration was not influenced by factors such as age, sex, race, or cause of death, there was a worrisome 50% increase in MNP concentration based on the time of death (2016 versus 2024).

This aligns with the observed exponential increase in MNP environmental concentrations over the past half-century (2). Particularly, 10 to 40 million tonnes of emissions of microplastics to the environment are estimated per year, with this figure expected to double by 2040 (3). Wind and water can redistribute microplastics and have since been reported in diverse locations from the deep sea sediments to our highest mountains (3). Microplastics are pervasive in the food we eat, the water we drink, and the air we breathe (3). Humans are exposed to MNPs through various routes, but their impact on various organ systems is not fully understood (4).

The current evidence base (largely based upon animal and cell culture studies) suggests that MNP exposure can lead to adverse health impacts via oxidative stress, inflammation, immune dysfunction, altered biochemical/energy metabolism, impaired cell proliferation, abnormal organ development, disrupted metabolic pathways, and carcinogenicity (4). These can lead to direct or indirect consequences to various organ systems, including respiratory, gastrointestinal, cardiovascular, hepatic, renal, nervous, reproductive, immune, endocrine, and muscular (4). Particularly, a recent study in *The New England Journal of Medicine* found that people with a carotid artery plaque in which MNPs were detected had a higher risk of myocardial infarction, stroke, or all-cause mortality (5). Additionally, inflammatory bowel disease (IBD) patients' stool contained about 1.5 times more microplastics than healthy controls, averaging 41.8 vs. 28.0 particles per gram of dry stool (6). However, the underlying mechanisms and whether long-term exposure to MNPs is associated with disease susceptibility is an area that requires further investigation.

Due to the higher concentration in the brain, the 3–5 times higher amount in brains with dementia, specific attention should be given to the nanoparticles <200 nm, predominantly polyethylene, found in the brain. In a study on fish, nanoplastics reduced swimming activity and hunting (predatory) performance (7). A study of mice exposed for 8 weeks led to learning and memory deficits, lower levels of synaptic proteins, and neuroinflammation (8). In human studies, the significance of elevated microplastic levels in patients with dementia remains unclear. Is dementia weakening the blood-brain barrier, allowing more microplastics to enter? Or do microplastics, once inside, trigger microinflammation and make it harder for the brain to clear proteins, potentially worsening neurodegeneration?

Given the widespread presence of microplastics in the environment, completely eliminating exposure is unrealistic. A more practical approach is to reduce the most significant sources of microplastic intake. Switching from bottled water to tap water could reduce microplastic intake from 90,000 to 4,000 particles per year, making it an impactful intervention (9). However, while reducing intake is a logical approach, it remains unclear whether this translates into a measurable reduction in microplastic accumulation within human tissues. Beyond bottled water, significant dietary sources of microplastics are alcohol and seafood.

Stopping the practice of heating food in plastic could be one of the most effective ways to reduce microplastic consumption. Tea bags are often plastic, and a study found that despite being labeled food grade released a total of 16 μm of micro and nanoplastics (2.4 million micron-sized particles 1–150 μm and 14.7 billion submicron plastic particles <1 μm) (10).

Additionally, food storage may contribute to microplastic exposure. A randomized crossover trial of canned foods showed a more than 1000% rise in urinary bisphenol A (BPA) levels after five days of daily canned soup intake (11). This suggests that limiting canned food consumption and opting for non-plastic or BPA-free packaged alternatives can effectively reduce exposure. These BPA spikes' duration and health impact remain unclear, warranting further research.

Highly processed foods, like chicken nuggets, contained 30 times more microplastics per gram than chicken breasts, highlighting the impact of industrial processing, which often uses plastics at some point (12). One RCT looking at depression outcomes showed that eliminating 21.76 servings/week of highly processed foods per week (often stored in plastics) had a reduction in depression >1 effect size (13). The study concluded that the reduction in depression was due to a more Mediterranean diet. However, it is possible that the diet also lowered microplastic intake, contributing to improved brain health, though this was not directly examined in the study (14).

Inhalation is another substantial source of exposure, with up to 62000 particles in male adults per year. A High-Efficiency Particulate Air (HEPA) filter removes up to 99.97% of airborne particles as small as 0.3 μm, which

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includes a significant amount of airborne microplastics, though data on whether this translates to meaningful changes in absorption and outcomes humans is lacking (15).

Avoiding plastic and opting for glass or stainless steel containers may reduce intake. Heating food in plastic containers, especially in the microwave, can release staggering amounts of microplastics and nanoplastics—up to 4.22 million and 2.11 billion particles per square centimeter in just three minutes (16). Even long-term storage at room temperature or in the fridge leads to significant plastic shedding. These plastics show toxic potential, with in vitro studies revealing up to 77% cell death in human kidney cells after prolonged exposure (16).

There is scarce evidence on the effective removal of microplastics once they have been ingested. One study of 20 individuals measured BPA in blood, sweat, and urine. BPA is a chemical compound used in the production of plastics, which is released when plastics degrade. 16 of the individuals had BPA identified in their sweat, with this being the only identified source of BPA in some individuals. This suggests that induced sweating could facilitate the removal of BPA, though further studies are required to investigate its efficacy and long-term implications (17). While some evidence suggests that sweat may facilitate the excretion of certain plastic-derived compounds like BPA, no direct research currently confirms its role in reducing the microplastic burden in humans. Further studies are needed to determine whether these strategies are effective in eliminating microplastics from the body.

Future research should prioritize establishing clear exposure limits and assessing the long-term health consequences of microplastic intake. Large-scale human studies are needed to determine the dose-response relationship between microplastic exposure and chronic health outcomes such as endocrine disorders and cognitive disease. Standardizing biomonitoring methods to track microplastic accumulation in tissues will also be essential for understanding their physiological impact and association with other diseases, ideally in cohort studies controlling for both intake variables like use of plastics, types of foods consumed, but also excretion (frequency of sweating in sauna and exercise). In parallel, studies should further evaluate the effectiveness of various reduction and elimination strategies.

One of the most hopeful aspects of the findings to date is the lack of correlation between age and microplastic accumulation, suggesting that despite ongoing environmental exposures, the body has mechanisms to clear these particles over time through sweat, urine, and feces. As methods for measuring microplastics in living humans improve, we can test the common-sense hypothesis that reducing intake of microplastics (e.g., drinking tap water, avoiding plastic tea bags, using metal or glass for cooking and storage, minimizing highly processed foods stored in plastic) and enhancing elimination may reduce accumulation in humans. In fish models, it takes approximately 70 days to clear 75% of accumulated brain microplastics, suggesting that decreased inputs and increased outputs must both be maintained for long enough durations to see measurable changes (18). As the knowledge increases, government-wide initiatives will help us reduce exposure.

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VIEWPOINT

Microplastics and mental health: The role of ultra-processed foods

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Keywords: Anxiety, depression, mental health, microplastic, ultra-processed foods

Ultra-processed foods now dominate the food supplies of high-income countries, with over 50% of energy intake coming from ultra-processed foods in the United States. Observational data has revealed that greater ultra-processed food consumption is associated with adverse mental health outcomes, while data from randomized controlled trials has demonstrated improvements to mental health following reduction in ultra-processed food intake. Ultra-processed foods are known to contain high concentrations of microplastics, largely due to both the processing and packing procedures. In light of recent findings which demonstrated alarming microplastic concentrations in the human brain, we propose that microplastics may partially mediate the adverse mental health effects of increasing ultra-processed food intake. In this viewpoint, we discuss the overlapping mechanisms for adverse mental health, paucity of research in the area, and propose a Dietary Microplastic Index (DMI) to study this potential relationship.

Using the Nova food classification system, ultra-processed foods are industrial formulations made almost entirely from substances extracted from foods, derived from constituents of foods, or synthesized in laboratories. Examples include instant noodles, carbonated drinks, and packaged foods (1). Ultra-processed foods now dominate the food supplies of high-income countries, such as the United States and Canada, and their consumption is rapidly increasing in middle-income countries (2). Particularly, the United States has one of the highest percent energy intake from ultra-processed foods at over 50% (3). This shift from whole foods to ultra-processed foods is largely driven by transnational food manufacturing, extremely profitable fast food corporations, and heavily promoted ultra-processed foods in the form of snacks (2).

A recent umbrella review in *The BMJ*—including nearly 10 million participants—found that people who consumed ultra-processed foods had a 22% higher risk of depression, 48% higher risk of anxiety, and 41% higher risk of poor sleep outcomes, among numerous adverse physical health outcomes (4, 5). On the contrary, evidence has demonstrated that those who adhere to a nutrient dense diet, primarily of unprocessed foods, are at a lower risk of adverse mental health outcomes (6). Beyond observational research, small randomized controlled trials have demonstrated moderate-to-large improvements in depressive symptoms with a Mediterranean diet compared to controls in those with depression (7). As such, from both observational and interventional research, there is a clear pattern between dietary intake and mental health.

The associations between ultra-processed foods and adverse mental health are complex and multifaceted. From a biological perspective, numerous mechanisms—largely identified through animal studies—are likely at play including inflammation, oxidative stress, epigenetics, mitochondrial dysfunction, the tryptophan–kynurenine metabolism, the hypothalamic-pituitary-adrenal axis, neurogenesis (via brain-derived neurotrophic factor), epigenetics, and chronic diseases such as obesity (8). This likely arises from their poor nutrient profiles, energy density, and the physical/chemical properties associated with industrial processing and packaging methods, which introduce bisphenols and microplastics as contaminants (4). Interestingly, microplastics share similar mechanisms for their adverse health effects via oxidative stress, inflammation, immune dysfunction, altered biochemical/energy metabolism, impaired cell proliferation, abnormal organ development, disrupted metabolic pathways, and carcinogenicity (9). With particular attention to the central nervous system, microplastics and nanoplastics can induce oxidative stress, which may cause cellular damage and increase vulnerability to neuronal disorders. Particularly, microplastics have been demonstrated to influence neurotransmitters such as acetylcholine, γ-aminobutyric acid, and glutamate, which are commonly implicated in neuropsychiatric disorders (9). Although, the above mechanisms are largely based upon animal and cell culture studies.

High concentrations of microplastics are found within ultra-processed foods, largely due to both the processing and packing process (10, 11). For example, foods like chicken nuggets contain 30 times more microplastics per gram than chicken breasts—highlighting the impact of industrial processing on the content of the food (12, 13). Further, ultra-processed foods are often stored and heated in plastic, which independently serve as a significant source of microplastic exposure. Particularly, some plastic containers can release as many as 4.22 million microplastic and 2.11 billion nanoplastic particles from only one square centimeter of plastic area within 3 min of microwave heating (14). Beyond microplastics, Bisphenol A (BPA), a chemical compound used in the production of plastics, which is released when plastics degrade, is commonly found in packaging for ultra-processed foods (15). Therefore, the consumption of ultra-processed foods may serve as a significant risk factor for microplastic and BPA accumulation within humans.

Up until recently, most research on microplastic accumulation and human health has focused on correlations between physical health outcomes such as myocardial infarction, stroke, irritable bowel disease, and death (9, 16, 17). It was not until a study in *Nature Medicine* found that the human brain contains approximately a spoon's worth of microplastics, with levels three to five times higher in those with a documented dementia diagnosis (although this does not demonstrate causality) (18). The microplastics in the brain were smaller ($<$200 nm), most often polyethylene, and were 7 to 30 times higher than those in other organs such as the liver or kidney. This study also found a 50% increase in microplastic concentration based on time of death, from 2016 to 2024, which parallels the ongoing rise of ultra-processed foods available. For BPA, associations have been found with mental disorders such as autism, depression, and anxiety (19, 20). No evidence currently exists (in humans) for microplastic accumulation and other mental health outcomes, partially due to the difficulty in quantifying microplastic exposures from an observational perspective and ethics surrounding microplastic exposure from an interventional perspective.

The accumulation of a substantial quantity of microplastics in the brain and throughout the body raises significant health concerns. Emerging evidence suggests potential effects on immune function, genetic

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stability, and endocrine regulation, making it reasonable to expect that such widespread deposition could have adverse impacts on both mental and physical health (21, 22). As ultra-processed foods, which contain significant microplastic content, represent over half of energy intake in the United States, with simultaneous rise in the rates of depression, it is imperative that this link be further examined (3, 23).

The first study that propelled the field of Nutritional Psychiatry was the SMILES trial (24). It was a 12-week, parallel-group, randomized controlled trial of adjunctive dietary intervention for the treatment of moderate to severe depression. Beyond depression, the participants were confirmed to have a "poor" dietary quality through the use of the Dietary Screening Tool (DST) (25). In this study, the dietary intervention largely focused on replacing nutrient poor, ultra-processed foods with nutrient dense, unprocessed alternatives. Sixty-seven people were randomized to a dietary intervention ($n = 33$) or control ($n = 34$) setting, with depression symptomatology, as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS), serving as the primary endpoint at 12 weeks. The dietary support group eliminated 21.76 processed foods per week and demonstrated significantly greater improvements at 12 weeks on the MADRS than the control group, whereby remission was achieved for 32.3% and 8.0% of the intervention and control groups, respectively, with a number needed to treat of 4.1. While the aim of this study was to improve the overall nutritional value as an intervention, there was likely a direct reduction in microplastic intake as a result of these aforementioned substitutions. However, as microplastic exposure was not directly measured, this remains a hypothesis requiring further investigation.

Retroactively, for the SMILES trial (24) or the numerous other randomized controlled trials (7) that have since been conducted in the field of nutritional psychiatry, it would be of utmost value if post-hoc analyses could be conducted estimating the change in microplastic content due to dietary interventions, and their subsequent effect on various mental health outcomes. This may become increasingly possible as more research quantifying the microplastic content of various ultra-processed food items is readily available (12, 13). From an observational perspective, no nutritional population-based surveys currently estimate or track microplastic intake via diet, which precludes analysis of long-term microplastic exposure via diet and adverse mental health outcomes. Perhaps, similar to the Dietary Inflammatory Index (DII), which is used to assess the inflammatory potential of a person's diet based on the foods they consume (26) or the Nova food classification system, which categorizes foods based on the extent and purpose of industrial processing (1), a Dietary Microplastic Index (DMI) can be developed or integrated into existing dietary-based risk indices, to assess the microplastic content and risk of accumulation based on the foods consumed.

Overall, as the levels of ultra-processed foods, microplastics, and adverse mental health outcomes simultaneously rise, it is imperative that we further investigate this potential association. After all, you are what you eat.

Author Contributions

Nicholas Fabiano was responsible for the conceptualization and writing the original draft. All authors participated in review/editing and approved the final version of the manuscript.

Author Disclosures

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VIEWPOINT

Depression: A malady of the self, arising from stress responses gone awry

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Major depression is one of the most significant disorders of our time. It is a heterogeneous, common, and complex disorder of gene–environment interactions, with multiple subtypes, including patients with melancholic or atypical features, that appear to stem from distinct clinical and physiological substrates. Stress is a disruptor of homeostasis and may pathologically extend into depression, particularly when adaptive responses become dysregulated. An integrated treatment approach, combining psychotherapy and pharmacotherapy, should target both the behavioral patterns and physiological underpinnings of depressive disorders.

Before describing how a stress response can evolve into clinical depression, I would first like to briefly discuss the scope of the problem and elucidate the clinical manifestations of depressive illnesses that can be construed as stress responses run awry.

Scope of the Problem

Clinically significant forms of depression affecting approximately 20% of individuals in the United States are likely to affect an equal number in populations around the world, depending on genetic characteristics and living conditions. The World Health Organization rates depression as the second most significant cause of disability worldwide and the greatest cause of disability in those under 45 years of age. While 60 million Americans have a major depressive illness, less than half are treated for depression with psychotherapy and pharmacotherapy, while the majority receive no treatment at all. In addition to causing great psychological anguish, disruption of families and interpersonal relationships, and the course of one's career (1, 2), the physiological manifestation of depression results in significant increases in the rate of premature systemic illnesses (3), such as premature coronary disease (4, 5), stroke (6), diabetes (7, 8), and osteoporosis (9), and shortens the lifespan by as much as ten years (10).

Clinical Manifestations of Different forms of Depression Subtypes

One of the key presentations of major depressive disorder (MDD) is depression with melancholic features, a DSM-5 specifier of depressive disorders, which constitutes roughly 30% of patients who develop MDD (11). Melancholic depression often contradicts the term depression in that it is often a state of increased vigilance and anxiety, especially about the value of the self. Indeed, melancholic depression intrudes upon many of the components that define our humanity (10). It is associated with a negative; one could even say malignant transformation characterized by the anguish of feeling thoroughly worthless (12, 13). A second malignant transformation is the loss of the capacity to anticipate or experience pleasure and even to remember past moments in life that brought pleasure and gratification. It is as if one had led a life saturated by despair and self-hatred, during which nothing of value was accomplished and most important interpersonal relationships failed. Many individuals with melancholic depression feel that life has no meaning. Hence, melancholic depression contributes significantly to those who feel the existential distress of living a meaningless existence in a meaningless world. For these reasons, I refer to melancholic depression as a profound disorder of the self (13, 14).

Melancholic depression is associated with a variety of physiological disturbances that produce premature systemic illnesses and shorten lives by as much as ten years. In particular, they experience the premature onset of coronary artery disease, stroke, diabetes, and osteoporosis. Physiologically, they have activation of the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, significant central nervous system and peripheral inflammation, increased hemoconcentration and coagulation, and activation of the renin–angiotensin system (14, 15).

A second phenotype of major depression seems, in many ways, the antithesis of melancholic or typical depression. It is called in the DSM-5 Major Depressive Disorder with atypical features in the DSM-5, and it is commonly referred to as atypical depression (10, 11). It is often associated with feeling out of touch with self and significant others, including spouses and children, feelings of emptiness, increased appetite, increased sleep, daytime fatigue and listlessness, and a significant incapacity to experience pleasure, anticipate a positive future, and consequent intense dysphoria. Patients with atypical depression have decreased levels of hypothalamic corticotropin-releasing hormone (CRH), plasma cortisol (16), increased plasma glucose, and increased inflammation (17), in part due to the weight gain occasioned by their increased appetite. In contrast to patients with melancholic depression, individuals with atypical depression feel worse in the evening than in the morning, when the stress response is relatively quiescent.

Rene Spitz made observations about infants and very young children who lived in orphanages. Although they initially responded to being left alone or hungry, as time progressed, they stopped showing overt emotional responses to deprivation. They seemed to lose interest in others and their environment. It was as if they had shut down their perceptual and emotional faculties to avoid the great distress of their impoverished state (18). Nonhuman primates separated from their mothers at birth and raised by those who were not much older than themselves showed emotional withdrawal and had very low cortisol levels (19). This presentation may share features of an extreme variation of atypical depression.

What is Stress?

Hippocrates wrote that we are all subject to disturbing forces that upset our equilibrium (20). We survive these disturbing forces because there are restorative forces that can re-establish homeostatic equilibrium. He called these restorative forces *Vis Medicatrix Naturae*, the healing power of nature (21). We now call the disturbing forces stressors, the balance homeostasis, and the healing forces adaptive responses (22).

Stress is a state of threatened homeostasis. Threats to homeostasis represent stressors that must be resolved to sustain homeostasis and viability. Uncontrollable stressors that threaten survival and are noxious promote the most profound stress responses. Stressors are almost always associated with increased vigilance and anxiety that represent calls to action, which often reflect conscious and unconscious sources. The stress

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response aims to promote survival and effective homeostatic set points. Thus, the stress response is one of our critical adaptative responses (23). Other adaptive responses include the immune response, which is responsible for providing effective answers to injury and infection. Like the stress response, the immune response can also run awry, manifested as autoimmune phenomena, characterized by immune responses to our own tissues and organs. Chronic stress decreases lifespan by many of its actions. In depression, a maladaptive stress response disturbs neuronal functions such as mood, cognition, and behavior, as well as multiple physiological responses throughout the body, which can predispose to premature systemic illness and shorten lives.

What Constitutes a Healthy Stress Response?

I chose an example of hikers in the woods who were notified that there was a forest fire nearby, which could threaten their survival. Their principal behavioral responses are hypervigilance, anxiety, and doing whatever they can to escape the nearby threat. It is essential that the hikers remain focused on the threat and are not distracted. One of the key means of ensuring that distraction does not occur is a substantial decrease in their propensity to be tempted by pleasant stimuli such as a beautiful site, food, sex, sleep, or other sources of gratification.

These adaptations are associated with significant changes in cognitive functions. There is a pronounced shift away from complex, sequence-dependent processes, and they focus exclusively on avoiding the dangers of the fire and getting back to safety.

Multiple physiological processes are also set into motion to prime metabolic, inflammatory, and coagulation processes. Blood glucose rises to assist the stressed brain. There is premonitory inflammation before injury occurs, so prepare for this contingency in advance. Blood clotting increases to prevent the sequalae of a possible hemorrhage occurring in a dangerous situation—their blood pressure, pulse rate, and cardiac contractility increase. The renin–angiotensin system is also premonitorily activated to protect from precipitous drops in blood pressure that might occur during dangerous situations. Unfortunately, these changes also occur reflexively in the context of psychological stressors such as test taking and defending one's ideas in classroom or work situations.

The question arises regarding why disturbances such as insulin resistance, increased plasma glucose levels, inflammation, and activation of the renin–angiotensin system occur as components of a normal response to physical or emotional stressors. In our early evolutionary history, the key stressors were conflicts regarding competition for mates, protecting the young, being hunted, and facing starvation. In these contexts, perceiving the possibility of danger meant that premonitory physiological changes adaptively occurred to prepare for possible injuries incurred during life-threatening circumstances. These early adaptations that have persevered into the present make significant contributions to the morbidity and premature mortality that occur in the of frequent or sustained psychological or physical stress (22).

Fortunately, when the hikers reach a safe place insulated from the dangers of a forest fire, their stress responses fundamentally resolve. They can think more clearly and in complex terms, enjoy everyday pleasures, their blood glucose levels return to normal, and resolve their inflammatory and coagulation processes. If these stress responses do not resolve but evolve into exaggerated and maladaptive behavioral and physiological states, depression can emerge, especially in genetically susceptible individuals.

The Interface between the Stress Response and Major Depression

During stress, anxiety and alarm are sufficient to promote effective action to cope with the danger and minimize harm, and thus, do not interfere with the capacity to maximize the likelihood of effective coping and survival (23). In MDD with melancholic features, fear, anxiety, and alarm are markedly more intense than during a normal stress response, producing hopelessness and anxiety that interfere with the capacity to take steps to overcome the depression. Thus, the symptoms of melancholic depression lock in the state, and depressive episodes can persist for long periods.

The stress response is associated with sufficient anxiety to promote substantial and practical efforts to avoid being hurt without interfering with adaptive functioning. In melancholic depression, fear, anxiety, and alarm can be profoundly greater than during stress, produce anguish and hopelessness, and interfere with the capacity to fight off depression.

In stress, cognition shifts from a propensity to tackle and deal effectively with complex situations and problems to instinctual or automatic actions that had previously worked in the context of manifest danger. In melancholia, concentration is impaired, and overall cognitive function diminishes. Moreover, cognition is often dominated by obsessive, ruminative preoccupations regarding fear, the deficiencies of the self, and the gloomy expected outcomes for such a defective self.

In a healthy stress response, there is a palpable decrease in the capacity to respond to pleasurable stimuli. This serves as protection against unwanted distractions. The decreased propensity to react to pleasant stimuli is insufficient to lead to demoralization that could interfere with an adequate stress response. In melancholia, the decrease in the capacity to anticipate or experience pleasure is pervasive and profound, leading to an incapacity to enjoy anything or remember ever being happy.

In response to stress, there is a tendency toward a decreased appetite and a decreased propensity to sleep, which allows total focus on the threat at hand. Stress does not usually lead to weight loss and loss of sleep and is ordinarily not nearly as severe as it is in melancholia. Melancholic patients lose their appetite, which can be life-threatening in the elderly, who also often have severe insomnia and marked early morning awakenings.

Activation of the CRH system, the sympathetic nervous system, and plasma glucose levels increase in a normal stress response to support the stressed body and brain. In addition, inflammation and coagulation are an inherent part of the normal stress response as the activation of stress hormone secretion to premonitorily anticipate and more effectively respond to injuries or hemorrhage occurring during a dangerous situation. The renin–angiotensin is also activated premonitorily. As mentioned, these changes occur to effectively anticipate loss of blood pressure due to hemorrhage or other factors during a stressful situation and promote survival. Stress–hemoconcentration is elevated in major depression and it is normalized by antidepressant treatment (15).

Melancholic depression is associated with a sustained elevation in the activity of the CRH system and the sympathetic nervous system, insulin resistance, increased plasma glucose levels, sustained inflammation in the brain and the periphery, and increased coagulation. Their sustained activation contributes to premature systemic diseases and premature deaths.

Taken together, the changes in melancholic depression indicate a stress system that has run awry, is excessively activated and is physiologically dysregulated.

We know less about atypical depression than we do about melancholia. We have shown, however, that patients with atypical depression have decreased activation of the CRH system and the pituitary–adrenal axis. In contrast to melancholia, their excessive sleep, daytime fatigue, and loss of a sense of connection to themselves and others suggest a stress system that is relatively inactivated.

Individuals with MDD and atypical features also manifest increased inflammation (17), noted earlier to reflect, in part, their weight gain secondary to their increased appetites. It is not known the extent to which distinct features of melancholic and atypical depression result in premature systemic illness and early death of patients with depression. While the physiological stigmata of melancholia are pretty likely to lead to these sequelae, it is unclear, except for inflammation, what might contribute to premature death in those with atypical depression.

The substantial data suggesting that MDDs reflect dysregulation of the stress response strongly support the validated premise that depressive illness responds best to a combination of psychotherapy and psychopharmacology. Stressful stimuli activate critical components of the stress system involved in the pathophysiology of affective illness and change its structure and function. Psychotherapy often helps in resolving maladaptive behaviors that promote interpersonal conflict and difficulties in work that, if they remain unchanged, can override the positive effects of psychopharmacology intervention.

An example of dysregulation of the stress system that seems relevant to the pathophysiology of melancholia is the loss of as much as 40% of

the volume of the subgenual prefrontal cortex in depression, particularly melancholia (24). The subgenual prefrontal cortex is involved in multiple components of the depressive syndrome. It estimates the likelihood of punishment or reward. It restrains the amygdala in its generation of fear. It primes the nucleus accumbens pleasure and reward center and restrains the CRH and sympathetic nervous systems. All of these are critical components of depressive illness.

The mechanisms by which a dysregulated stress response promotes and sustains depressive illness are currently being elucidated. We now know that major depressive illness is a neurodegenerative disease and that tissue is lost during the depressed phase not only in the subgenual prefrontal cortex but also in other prefrontal sites, such as the dorsolateral prefrontal cortex (10).

The role of stress in the pathophysiology of melancholia is better understood than in atypical depression. Stress produces excess cortisol and promotes CNS inflammation, which can be neurotoxic. Stress also downregulates the production and levels of brain-derived neurotrophic factor, whose deficiency is a crucial component of depressive illness and contributes to many of its stigmata, including not only lost neuroprotection and neuronal damage but decreased neurogenesis and neuroplasticity, also considered to be pathogenic factors in depressive illness.

Atypical depression occurs earlier in life than melancholia, is more often associated with childhood trauma, and tends to run a more chronic course. The downregulation of the stress response, which seems to occur in atypical depression, may produce behavioral withdrawal and suppression of overt emotionality as a defense against overwhelming pain. The downregulation of cortisol activity and attentiveness to external stimuli in nonhuman primates separated from their mothers at birth may provide a clue about the pathologic implications of a suppressed system. Low cortisol levels themselves can be associated with behavioral withdrawal and excessive fatigue. Future studies will likely uncover the behavioral and physiological consequences of a suppressed system and the mediators responsible for establishing and sustaining such a state.

I suggest that integrated treatment approaches, combining psychotherapy and pharmacotherapy, should target both the behavioral patterns and physiological underpinnings of depressive disorders and be tailored to address either decreased or increased stress responses according to MDD subtypes.

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BENCH TO BEDSIDE

Therapeutic potential of liver X receptor beta in depression and anxiety

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Liver X receptors (LXRs), particularly LXRβ, are emerging as crucial players in the translation of basic neuroscience to clinical psychiatry. These nuclear receptor transcription factors, initially known for their roles in cholesterol metabolism and inflammation, are now revealing promising connections between molecular mechanisms and psychiatric symptoms. This review highlights recent breakthroughs in understanding LXRβ's regulation and function in behaviors relevant to depression and anxiety, derived from studies using animal paradigms that capture specific features of these disorders. We explore how these preclinical findings are shaping our comprehension of mood-related behaviors at the molecular level and potentially paving the way for innovative therapeutic strategies. As a ligand-activated transcription factor, LXRβ represents a novel target for drug development, potentially bridging the gap between bench discoveries and bedside treatments for neuropsychiatric disorders. We discuss the challenges and opportunities in translating LXRβ research into clinical interventions, emphasizing the potential for personalized medicine approaches in psychiatry. This bench-to-bedside article underscores the importance of LXRβ research in advancing our understanding and treatment of complex mental health conditions, while acknowledging the nuanced interpretation required when extrapolating from animal studies to human disorders.

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Historical Perspective: LXRβ

Liver X receptors, LXRα and LXRβ, are members of the nuclear receptor family of ligand-activated transcription factors (1). The first cloned member, initially named RLD1 and liver X receptor (2, 3), was later renamed LXRα. Our laboratory discovered LXRβ, originally calling it OR-1 (4). Other labs simultaneously identified it under various names: UR (5), NER (6), and RIP-15 (7). Its similarity to LXRα led to its current name, LXRβ.

LXRα is well-known for its role in cholesterol homeostasis, with both receptors often dubbed master regulators of this process (8, 9). Oxysterols, which are oxygenated forms of cholesterol, serve as natural ligands for LXRs. While LXRs are most recognized for their influence on cholesterol homeostasis, LXRβ's functions extend far beyond. It regulates various transport mechanisms, including aquaporins for water transport (10–12), GLUT4 for glucose transport (13), MCT8 and MCT10 for thyroid hormone transport (14), and ApoE and ABC transporters for cholesterol transport (15). This diverse involvement explains LXRβ's wide-ranging effects throughout the body.

Research on LXRα has primarily focused on organs involved in lipid metabolism, such as the liver, intestine, adipose tissue, and within the immune system, particularly in macrophages (16). In contrast, LXRβ shows a broader tissue distribution. While its liver expression is minimal, LXRβ is well-expressed in immune system cells, CNS glial cells, the colon, gallbladder, pancreatic islets, retina, and inner ear (17–23). It is also widely expressed in fetal brain neurons (24, 25). Both LXRα and LXRβ are present in reproductive tissues like the ovary, testis, prostate epithelium, and epididymis, where they play significant roles (26–29).

LXRs form heterodimers with retinoid X receptors (RXRs) and bind to specific DNA response elements called DR4s. These are direct repeats of the half-site sequence 5′-G/AGGTCA-3′, separated by four nucleotides, also used by thyroid hormone receptors (3). Our research has shown that LXRβ protects neurons in both central and peripheral nervous systems. This protection extends to dopaminergic neurons in the substantia nigra (30), large motor neurons in the spinal cord's ventral horn (31, 32), epithelial cells of the choroid plexus (11), retinal ganglion cells (22), and spiral ganglion neurons (23). Recent reviews have thoroughly explored LXRs' role in neurodegenerative diseases like Alzheimer's disease (AD) (8, 33), Parkinson's disease (PD) (34, 35), amyotrophic lateral sclerosis (ALS) (36), and multiple sclerosis (MS) (37).

Role of LXRβ in Depression

Studies have demonstrated LXRβ's protective effects against depression-like behaviors in rodents, influencing neurons, microglia, oligodendrocytes, and astrocytes (Table 1). In rats exposed to chronic unpredictable stress (CUS), hippocampal LXRβ levels decrease. Treatment with the LXR agonist GW3965 reduces depression-like behavior and improves hippocampal neurogenesis in these rats (38). LXR's inhibition of microglial activation and neuroinflammation is a crucial protective mechanism, as seen in various injury paradigms (39–43). Several studies show that GW3965 treatment can modulate microglial status and suppress neuroinflammation, thereby improving emotional and cognitive functions as well as reducing depression-like behaviors in CUS-induced and other experimental paradigms (44–47). Additionally, GW3965's stimulation of oligodendrocyte maturation and enhanced myelination may contribute to the antidepressant effects of LXR agonists (48).

While LXR's role in depression-like behaviors has been extensively studied in mice (Table 1), research on LXR in the human brain is limited. Only one study to date has explored this connection (49), identifying a link between impaired LXR signaling and schizophrenia. RNA sequencing of dysfunctional dorsolateral prefrontal cortex gray matter revealed gene expression patterns indicative of abnormalities in LXR-regulated lipid metabolism pathways in schizophrenia patients. The study concluded that aberrations in LXR/RXR-regulated lipid metabolism lead to decreased lipid content in the prefrontal cortex, correlating with reduced cognitive performance.

Role of LXRβ in Anxiety

Anxiety disorders are the most prevalent psychiatric conditions (50). Female mice lacking LXRβ exhibit anxiety-like behavior and impaired behavioral responses (Table 1) (51). These mice show reduced expression of glutamate decarboxylase (65+67), the enzyme responsible for GABA

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Table 1. Summary of LXRβ effects on depression-like and anxiety-like behaviors in experimental rodent paradigms

Neuropsychiatric-related behaviors	Experimental paradigm	LXRβ ligand	Effects	Reference
Depression-like	Chronic unpredictable stress (CUS) exposure in rats	GW3965	Regulation of hippocampal neurogenesis	(38)
	CUS and lipopolysaccharide exposure in mice	GW3965	Inhibits microglial M1 polarization and restores synaptic plasticity	(44)
	CUS exposure in mice	GW3965	Suppresses microglial activation and neuroinflammation in hippocampal subregions	(45)
	CUS exposure in mice	GW3965	Improvement of oligodendrocyte maturation and enhancement of myelination	(48)
	CUMS and corticosterone drinking paradigm in mice	T0901317	Suppresses neuroinflammation by inhibiting NF-κB signaling and NLRP3 inflammasome activation	(46)
Anxiety-like	LXRβ-deficient female mice	–	Decreased glutamic acid decarboxylase (65+67) in the ventromedial PFC	(51)
	LXRβ-deficient male mice	–	Abnormality in locomotor activity and exploratory behavior, demyelination	(52)
	Forced swimming stress exposure in mice	GW3965	Rebalancing excitatory and inhibitory neurotransmission	(54)
	Astrocyte-specific LXRβ-deficient mice	–	Impaired synaptic transmission in mPFC	(53)

synthesis, in the ventromedial prefrontal cortex (PFC). Further studies demonstrated that loss of LXRβ function results in abnormalities in locomotor activity and exploratory behavior, as well as anxiety-like symptoms (52). LXR is expressed in microglia, astrocytes, and oligodendrocytes in the adult mouse CNS (18). Intriguingly, specific deletion of LXRβ from astrocytes resulted in anxiety-like, but not depression-like behaviors in adult male mice (53). This work suggests that astrocytic LXRβ in the medial PFC plays a critical role in regulating synaptic transmission. In an experimental paradigm of stress-induced anxiety-like behavior, the LXR agonist GW3965 exerted anxiolytic effects by restoring the balance between excitatory and inhibitory neurotransmission through LXRβ signaling activation in the amygdala (54).

Role of LXRβ in Autism

Autism, now referred to as autism spectrum disorder (ASD), is a pervasive neurodevelopmental disorder. Defects in dentate gyrus neurogenesis appear to be implicated in the development of ASD-like behaviors. LXRβ-deficient mice exhibited early alterations in dentate gyrus neurogenesis and displayed autistic-like behaviors, such as deficits in social interaction and repetitive behaviors (55). Additionally, LXR agonist T0901317 attenuated social deficits and stereotypical behaviors in BTBR T+tf/J (BTBR) and valproic acid (VPA) experimental paradigms (56).

Improving hippocampal neurogenesis appears to be a novel strategy for ASD treatment (57). LXRβ signaling regulates neurogenesis and enhances cognitive function (58–63). In 2019, Theofilopoulos et al. illustrated that 24(S),25-epoxycholesterol, the most potent and abundant LXR ligand in the developing mouse midbrain, along with cholesterol 24S-hydroxylase (CYP46A1) overexpression, facilitated midbrain dopaminergic neurogenesis in vivo (64). Notably, the 15q11.2 copy number variation (CNV) containing the CYFIP1 gene is associated with autism and schizophrenia. In 2024, De La Fuente et al. recently established a connection between LXRβ deficiency and neurodevelopmental disorders (65). This study revealed that the strong interaction of LXRβ with 24(S),25-epoxycholesterol is essential for neuronal maturation, while low activation of LXRβ leads to maintenance of the neuronal precursor phenotype. The study delineates LXR-mediated oxysterol regulation of neurogenesis as a pathological mechanism in neural cells carrying the 15q11.2 CNV and provides a potential target for therapeutic strategies for associated disorders.

In 2024, Menteşe Babayiğit et al. demonstrated that there is no association between the identified LXRβ (rs2695121/rs17373080) single nucleotide polymorphism and ASD (66). The study cohort comprised 107 children with autism (aged 2-18 years) and 103 age-matched children without autism. Despite the negative genetic association their data revealed that, compared to healthy developing children, those with ASD exhibited significantly higher levels of total cholesterol, low-density lipoprotein, and triglycerides, alongside markedly decreased levels of 27-hydroxycholesterol, suggesting its potential as a diagnostic marker for ASD.

Concluding Remarks

The available evidence suggests that LXRβ plays a pivotal role in preventing CNS disease in experimental rodent paradigms. If these observations translate to humans, LXRβ could emerge as a novel therapeutic target for treating neuropsychiatric disorders, particularly depression and anxiety. However, additional basic research and clinical trials are imperative to ascertain whether novel drugs targeting LXRβ can be effectively utilized in the clinical treatment of neurological and neuropsychiatric diseases.

Declaration of Possible Conflicts of Interest

The contributors have confirmed that no conflict of interest exists.

Author Contributions

J.-Å. G. and XS conceived the review topic. XS wrote the draft and prepared tables. All authors revised the final manuscript and approved the final version.

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Brain Medicine

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RESEARCH REPORT

Blocking nitric oxide production for glioblastoma: A targeted therapeutic approach

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Glioblastoma (GBM) represents the foremost prevalent and aggressive form of primary brain tumor, characterized by high morbidity and mortality rates. Nitric oxide (NO) has been shown to have diverse effects on various cancers, including GBM. Our previous study has shown NO synthase (NOS) hyperactivation in GBM cell lines. GBM cell survival was reversed by the NOS-targeting pharmacological inhibition in vitro. The current work explores the impact of inducible and neuronal NOS (iNOS and nNOS) inhibitors, BA-103 and BA-101, respectively, on a glioblastoma xenograft model. Both agents mitigate nitrosative stress through distinct mechanisms. NOD-SCID mice were used to establish a subcutaneous xenograft tumor model with U-87 MG cells. BA-103 and BA-101 were administered to mice via intraperitoneal injections. Tumor metrics, including weight and volume, were assessed. Immunofluorescence and Western blots were conducted to assess nitrosative stress, tumor proliferation, and cell death. Treatment with the NOS inhibitors, particularly with BA-101, significantly reduced tumor volume in the xenograft model. A dose-dependent study with BA-101 identified 80 mg/kg as the most efficacious dose for GBM treatment. Combining BA-101 with the antitumor drug temozolomide (TMZ) synergistically reduced tumor size and significantly increased survivability in mice bearing TMZ-sensitive cells. Our findings suggest that targeting nNOS holds promise as a therapeutic strategy for GBM treatment.

Keywords: Apoptosis, brain, glioblastoma, iNOS, neuroscience, nitric oxide, nNOS.

Introduction

Glioblastoma (GBM) is the most malignant type of glioma (1). GBM is attributed to 14.5 % of all brain tumors and 48.6% of primary malignant brain tumors (2, 3). The expected median overall survival rate of persons with this kind of tumor is 6–14 months (4) and the annual incidences of GBM account for 3.19–4.17 cases/100,000 person/year (3, 5, 6). Some studies suggested that age and gender are important factors in glioma development (7, 8). The treatment approach varies depending on the type of tumor and typically involves a mix of surgery, chemotherapy, and radiation (9, 10). Despite decades of research, GBM remains a formidable and deadly cancer. Current treatment approaches face limitations, such as drug resistance, molecular heterogeneity, and aberrant activation of different signaling pathways (1, 11). Severe adverse effects of the treatments currently in use for patients with GBM also pose a serious problem (12, 13). This prompts an urgent need for new therapies. Available pharmacological agents also face the problem of crossing the blood–brain barrier (14). Some promising drugs for first-line treatment are currently under development (15, 16). The correct strategy for brain tumor treatment should be to target the selective pathways that can give long-term therapeutic effects (10).

Nitric oxide (NO) is a small gaseous molecule that plays a significant role in various biological processes (17). It is crucial in regulating vascular function (such as vascular permeability, vasodilation, and angiogenesis), neural system development, neurotransmission, smooth muscle relaxation, immune responses, and cytotoxic functions (18). We have shown that excessive NO is implicated in the development of many neurodevelopmental, neurodegenerative, and neuropsychiatric disorders (19–27). NO is synthesized by inducible, endothelial, and neuronal nitric oxide synthase (iNOS, eNOS, and nNOS, respectively) (17). Increased activity of NOS enzymes and nitrosative stress are major culprits for developing many cancers (28, 29). Meanwhile, NOS inhibitors have been reported to alleviate different kinds of cancers, such as metastatic melanoma (30), human breast cancer (31), ovarian cancer (32), oral cell carcinoma (33), head and neck cancer (34), colon cancer (35, 36), and others. The cellular phenotypes and behaviors are impacted by the elevated NO present in the tumor microenvironment. In GBM, elevated NO levels are associated with advanced stages and reduced patient survival rate (37). NO involvement in cancer was reported long ago (38), but its exact mechanism is controversial and vague (37).

Excessive NO concentration leads to increased nitrosative and oxidative stress, which results in DNA strand breakage by alkylation and deamination of the nucleic acid bases in DNA (39). Aberrant NO also inhibits the activity of DNA repair enzymes (40). These changes enhance the neoplastic transformation and inhibition of apoptosis, promoting cancer development (41).

NO can induce both protumorogenic and antitumorogenic effects depending on its levels and physiological conditions (42). In GBM, NO generation by tumor cells may facilitate a progrowth environment for tumor cell proliferation and neovascularization (42). In gliomas, iNOS and nNOS have been found to promote glioma stem cell growth (43), develop temozolomide (TMZ) treatment resistance, and modulate the immune response. NO is also known to inhibit apoptosis via S-nitrosylation or cyclic GMP-dependent pathways (44). NO can also inhibit catalase and cytochrome P-450 and can cause redox imbalance and oxidative stress (44). Identifying the molecules targeting NO and NO-affected molecular pathways in GBM could be a novel target for the brain tumor study.

Our previous in vitro experiments targeting iNOS and nNOS with inhibitors have shown a marked reduction in U-87 MG cell proliferation (45). The current study (Figure 1) was designed to assess iNOS and nNOS inhibition as a therapeutic approach for GBM in vivo. We also compared the efficacy of this approach with the well-known antitumor drug TMZ and evaluated the effects of the combined action of BA-101 and TMZ.

Results

NOS Inhibition Reduces Tumor Growth in GBM Mice

The effects of pharmacological inhibition of nNOS and iNOS on tumor size and volume in mice were studied compared to vehicle-treated mice. In this set of experiments, we treated the mice with NOS inhibitors for 8 days. BA-103 reduced tumor size when compared to vehicle-treated mice. BA-101 also significantly reduced tumor growth compared to the vehicle group. Furthermore, BA-101 inhibited tumor growth at a

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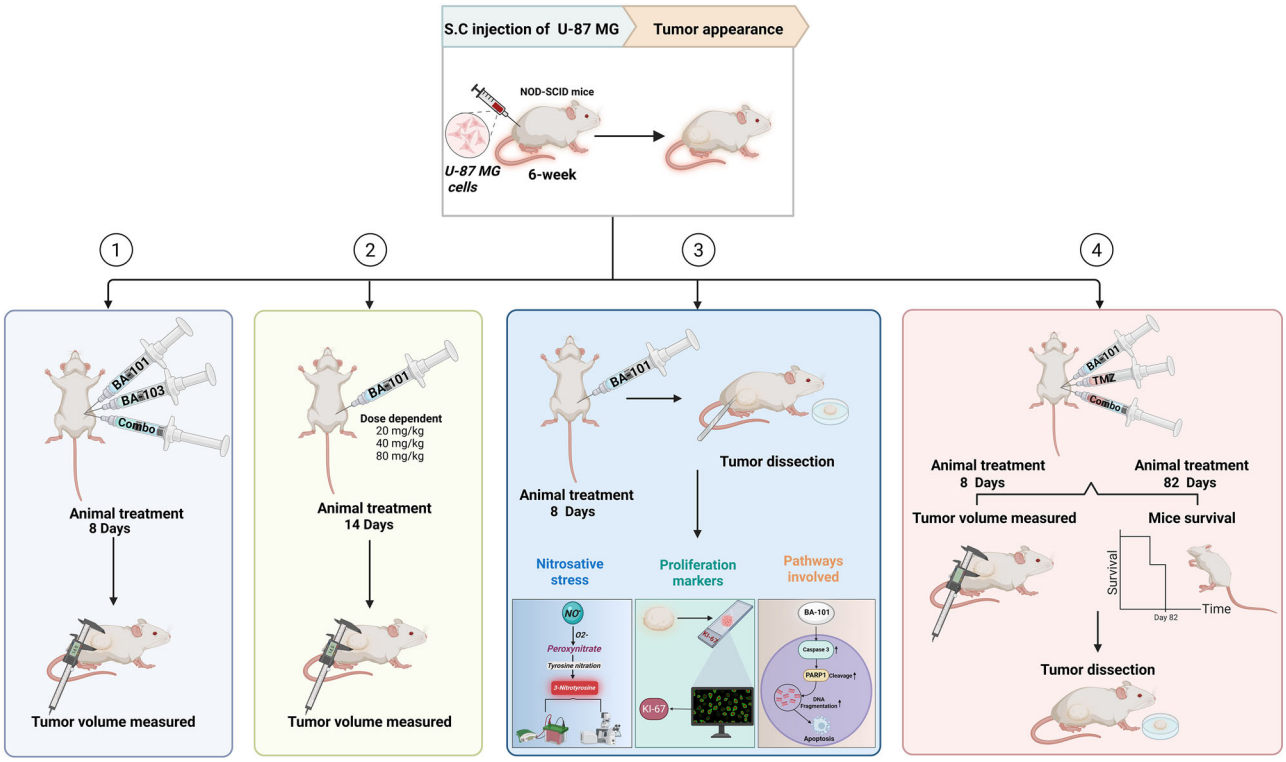

Figure 1. Schematic representation of the study. 6-week-old NOD-SCID male mice were injected with U-87 MG cells (1×10^6). Animals were treated with drugs or vehicles when tumors were developed. Tumor volumes were measured during different days of the experiment. The animals were sacrificed, and the tumors were isolated at the end of the experiment. WB and IF assays were performed to evaluate nitrosative stress and cell degradation processes.

considerably greater extent than BA-103. A combined treatment of BA-101 and BA-103 showed a marked reduction in tumor size compared to BA-101 or BA-103 treatment alone (Figure 2A and B). These results imply that both NOS inhibitors prevent tumor growth, but BA-101 was more effective than BA-103. Body weight analysis did not significantly change in all groups (Figure 2C). Tumor volume determination in real-time analysis showed that the tumors grew gradually in the vehicle group. Following the treatments with BA-103 and BA-101, the tumor growth was slower than in the vehicle group (Figure 2D).

The Dose-dependent Antitumor Effect of BA-101

We performed a dose-dependent study of BA-101, which appeared to be more effective in inhibiting the glioblastoma tumor volume than BA-103. Three doses of this compound were assessed, 20, 40, and 80 mg/kg. These treatments of BA-101 were given to mice daily for 14 days after the tumor size reached around 50 mm^3. All three doses of BA-101 reduced the tumor volume (Figure 3B and D) and tumor weight (Figure 3C) compared to the vehicle group and this effect was dose dependent with the most potent reduction of tumor growth at 80 mg/kg. The serial determination of the tumor volume on different days of the experiment showed that the tumor size in the vehicle group grew faster than in the treatment groups, reaching a statistically significant difference already on the fifth day (Figure 3D).

Effects of BA-101 on Cell Proliferation, DNA Damage, Nitrosative Stress, and Apoptosis in GBM Mice

Treatment of mice with 80 mg/kg BA-101 showed a reduction in the tumor proliferating marker Ki-67 levels compared to the vehicle group (Figure 4A). The nitrosative stress marker 3-Ntyr was reduced 2-fold in the BA-101–treated mice compared to the vehicle-treated group (Figure 4B and C). The DNA degradation marker, cleaved PARP1, appeared to be doubled in mice subjected to the BA-101 treatment compared to the vehicle group (Figure 4D). The apoptotic marker, cleaved caspase 3, was also significantly increased by the BA-101 treatment (Figure 4E). These results show that BA-101 treatment effectively reduced tumor proliferation and nitrosative stress while promoting DNA damage and apoptosis.

Effects of the Combined Treatment with BA-101 and TMZ on Tumor Growth

Then, the efficacy of BA-101 was compared to the TMZ, the gold standard of glioblastoma chemotherapy (46). We treated the mice with tumors daily for 8 days with BA-101 or TMZ or in combination with both (TMZ and BA-101). BA-101 and TMZ alone significantly reduced tumor size at a similar extent. However, treatment of GBM mice with the combination of TMZ and BA-101 provided a dramatically more significant reduction in the tumor volume than in the vehicle-treated groups (Figure 5A and B). Thus, tumor volume in the BA-101 + TMZ group of mice was reduced 6-fold, while in the BA-101 and TMZ groups, the reduction reached 50% and 60%, respectively. Real-time tumor volume analysis revealed consistent growth in the vehicle-treated group, whereas treatment with BA-101, TMZ, or their combination significantly reduced tumor growth. The most pronounced effect was observed in mice receiving the combination therapy (Figure 5C). We also tested the survival of mice after treatment with BA-101, TMZ, and the combination of BA-101 and TMZ. In the survival study, we treated the tumor-bearing mice with BA-101 daily and TMZ for 5 days a week in a 2-weeks-on, 2-weeks-off cycle until the mice reached the end of their survival period. The expected number of survival days (probability of survival) was the highest in the combo treatment with BA-101 and TMZ compared to the treatment of GBM mice with both the vehicle and either of these drugs alone (Figure 5D).

Materials and Methods

Materials

Primary antibodies anti-Ki-67 (AB16667) from Abcam, anti-cleaved caspase 3 (#9661) and secondary antibodies, anti-rabbit Alexa fluor 594 (#8889), anti-mouse Alexa Fluor 488 (#4408), Horseradish peroxidase (HRP)-conjugated anti-rabbit (7076S), HRP-conjugated anti-mouse (7074S), ProLong Gold Antifade with the nucleus marker DAPI

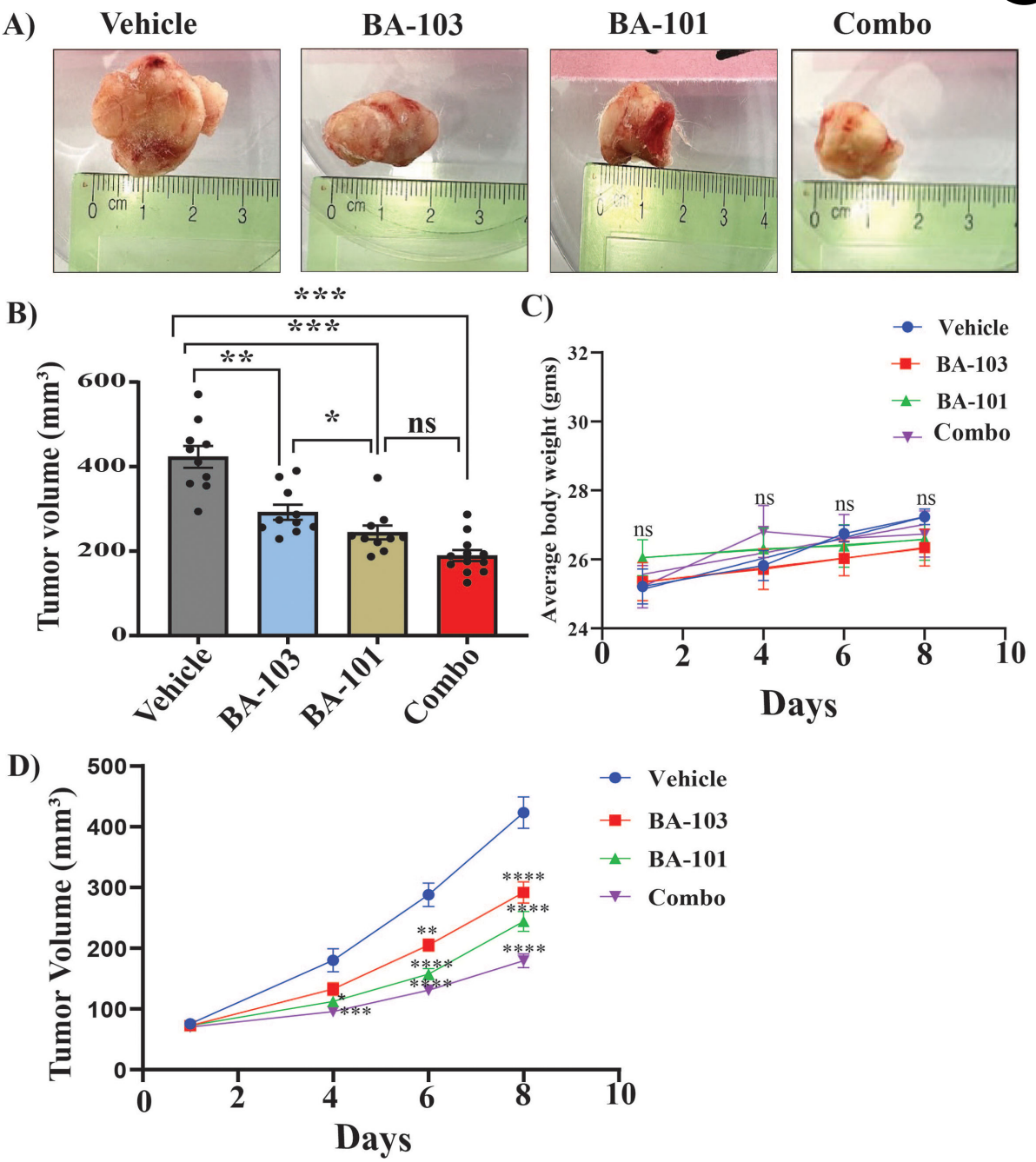

Figure 2. NOS inhibition prevents tumor growth in glioblastoma. (A) Representative tumor images in the Vehicle ($n = 10$), BA-103 ($n = 10$), BA-101 ($n = 10$), and BA-101 + BA-103 (Combo) ($n = 12$) groups of mice. (B) Statistical analysis of tumor volume in the groups mentioned above. (C) Statistical analysis of the dynamics of body weight changes in the above groups of mice during the experiment. (D) Statistical analysis of the dynamics of tumor volume changes in mice treated with vehicle ($n = 10$), BA-103 ($n = 10$), BA-101 ($n = 10$), and BA-103 + BA-101 ($n = 12$) during the experiment. Data are presented as mean ± SEM. $^{****}P < 0.0001$, $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, and ns, not significant.

(#8961), and protease phosphatase inhibitor cocktail (#5872) were purchased from Cell Signaling Technology (Danvers, MA, USA). Primary antibody anti-3-nitrotyrosine (3-Ntyr) (AB110282) was procured from Abcam (Cambridge, UK). Primary antibodies, anti-PARP1 (SC-56196) were purchased from Santa Cruz Biotechnology Inc. Other general chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and Bio-Rad Laboratories (Hercules, CA, USA).

The chemical identities of compounds BA-101 and BA-103 will be made available upon patent issuance. Patent applications covering the novel therapeutic use of these previously known molecules have been filed. Researchers interested in obtaining the compounds for research purposes after patent issuance should contact the corresponding author. We truly believe in data reproducibility and eager to uncover the names of the molecules as stated above.

Animals

All animal experiments were conducted under the guidelines of the Institutional Animal Care Committee of the Hebrew University of Jerusalem and Use Committee and the Association for Assessment and Accreditation of Laboratory Animal Care International. The ethical approval

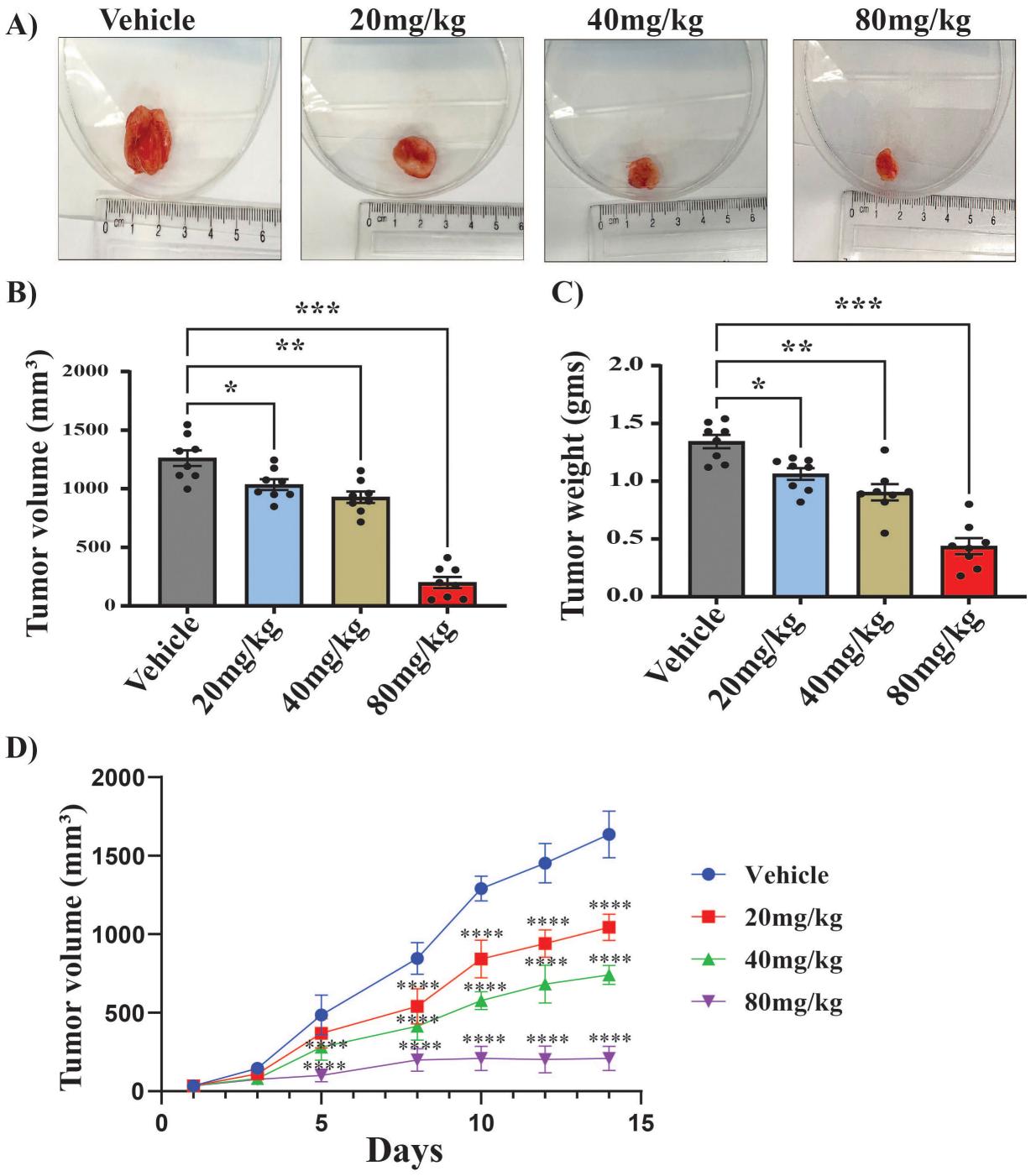

Figure 3. Dose-dependent treatment with BA-101. (A) Representative tumor images after dissection of the tumors in the dose–response study of BA-101. (B) Statistical analysis of tumor volume in mice treated with vehicle, and 20, 40, and 80 mg/kg of BA-101. (C) Statistical analysis of tumor weight in mice treated with vehicle, and 20, 40, and 80 mg/kg of BA-101. (D) Statistical analysis of tumor growth comparison in mice treated with vehicle ($n = 8$), and 20 mg/kg ($n = 8$), 40 mg/kg ($n = 8$), and 80 mg/kg of BA-101 ($n = 8$) on different days during the treatment. Data are presented as mean ± SEM. $^{****}P < 0.0001$, $^{***}P < 0.001$, $^{**}P < 0.01$, and $^{*}P < 0.05$.

(IACUC-MD-23-17231-5) was granted by the Hebrew University of Jerusalem. This study is reported under ARRIVE guidelines. Five-week-old NOD.CB17-Prkdc-scid/NCrHsd male mice were purchased from Envigo.

Glioblastoma Cell Line

Uppsala 87 Malignant Glioma (U-87 MG) cell line was obtained from the American Type Culture Collection (ATCC) and maintained in Dulbecco's modified Eagle medium (DMEM, Gibco 41965-039), 10% fetal bovine serum (FBS, Gibco 10270-106), 1% penicillin/streptomycin, 10,000 U/mL (Pen/Strep, Gibco 15140-122) in the humidified atmosphere (37°C, 5% CO_2).

Generation of Subcutaneous Glioblastoma Xenograft Model and Drug Treatment

Subcutaneous glioblastoma-bearing mice were obtained by subcutaneous injection of 1×10^6 U-87 MG cells in 100 μL PBS into the flanks of

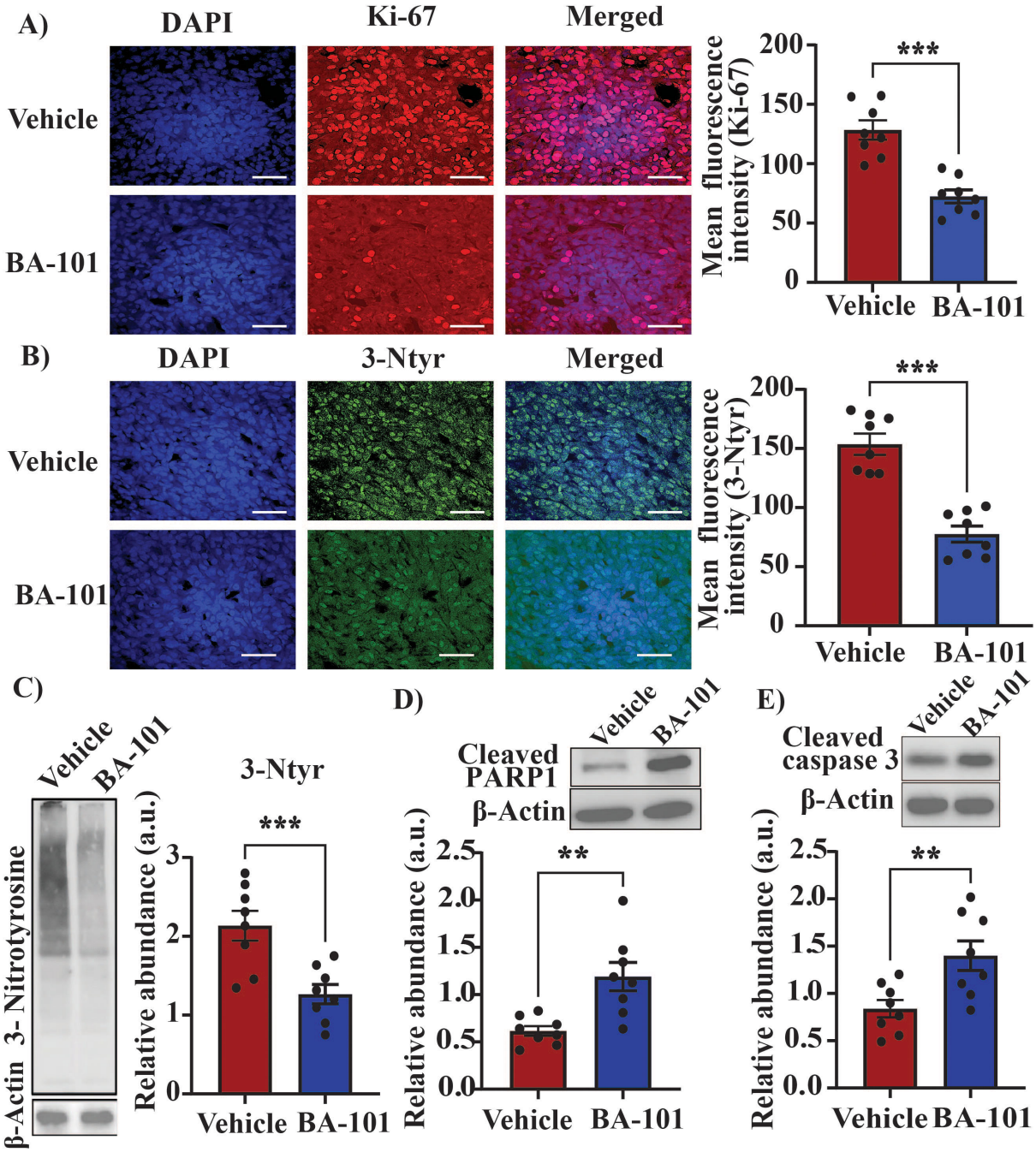

Figure 4. NOS inhibition with BA-101 induces apoptosis and reduces nitrosative stress. (A) Left: Representative confocal images of Ki-67 and DAPI in tumor sections of mice with Vehicle and BA-101(80 mg/kg) groups. The images were captured at 40 × magnification. Right: Statistical analysis of the mean fluorescence intensity of Ki-67 in both groups. (B) Left: Representative confocal images of 3-Ntyr and DAPI in tumor sections of mice of Vehicle and BA-101 groups. The image was captured at 40 × magnification. The scale bar in all images = 50 μm. Right: Statistical analysis of the mean fluorescence intensity of 3-Ntyr in both groups. (C) A representative WB image of 3-Ntyr and its quantitative analysis in Vehicle and BA-101 groups of mice. (D) A representative WB of DNA degradation marker PARP1 and its quantitative analysis in Vehicle and BA-101 groups. (E) Representative WB of cleaved caspase 3 protein and its quantitative analysis in Vehicle and BA-101 groups of mice. Data are presented as mean ± SEM. $n = 8$ in each group. $^{***}P < 0.001$, and $^{**}P < 0.01$.

6-week-old male NOD.CB17-Prkdc-scid/NCrHsd (NOD-SCID) mice. Then, 2–3 weeks after tumor cell implantation, when the average tumor size reached approximately 50 mm^3, mice were randomly divided into four groups, with 6–10 mice per group. Animals were treated intraperitoneally with a vehicle, BA-103 (10 mg/kg), BA-101 (80 mg/kg), or TMZ (10 mg/kg) in 100 μl of PBS containing 5% DMSO. All mice were sacrificed after the tumor size reached 1.5 cm in either of the dimensions. Tumor tissues were surgically excised, either stored at −80°C or fixed with 4% paraformaldehyde solution, dehydrated, and used for cryosectioning.

Tumor Growth and Probability of Survival

The tumor growth was assessed by measuring the tumor weight and volume. The mouse body weight and tumor size were measured every other day during the experiments. The tumor volume was measured with a digital caliper and calculated with the following formula: tumor

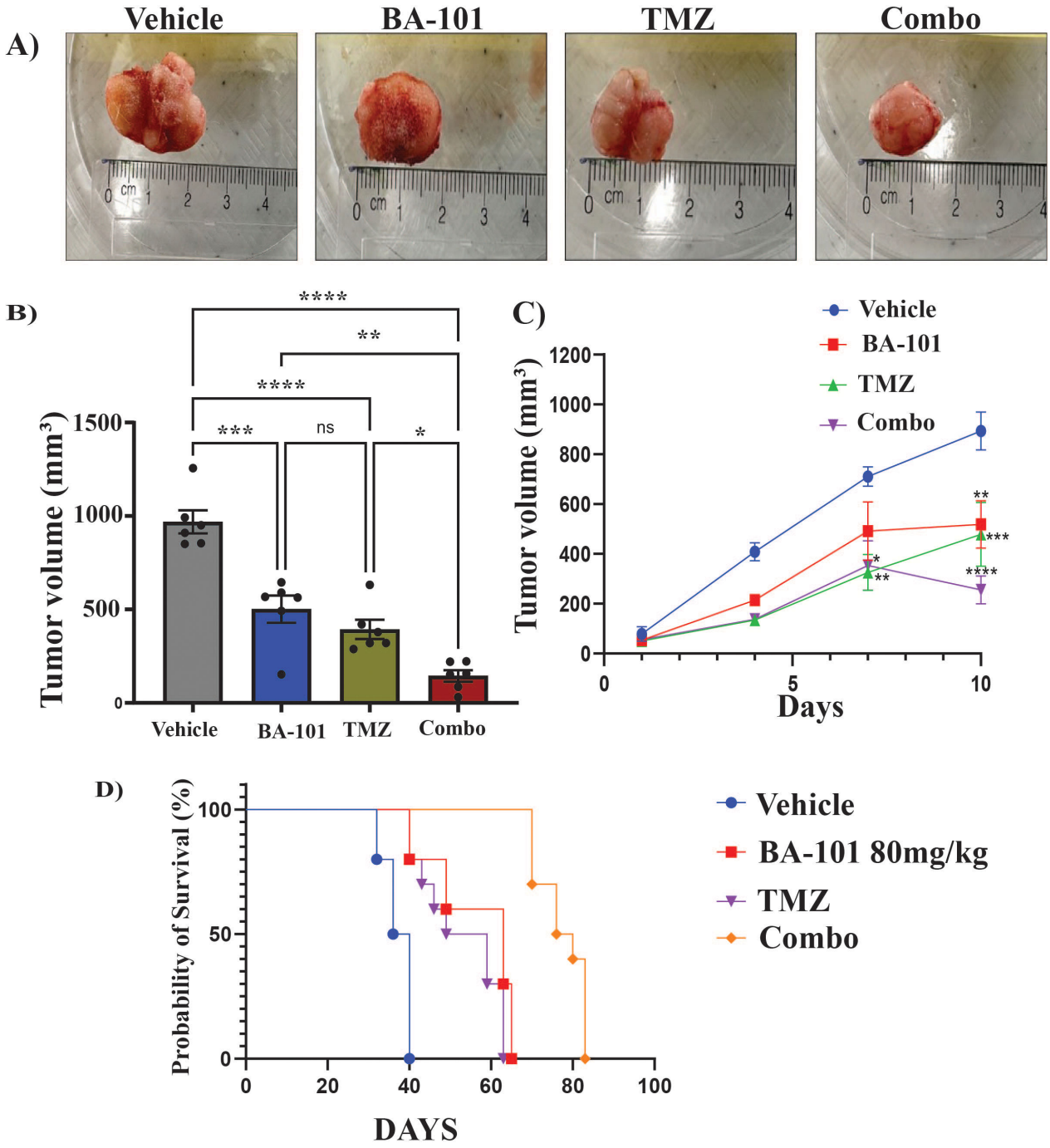

Figure 5. Combo treatment of TMZ and BA-101 increases survivability. (A) Representative tumor images after dissection in Vehicle, BA-101 (80 mg/kg), TMZ, and BA-101 + TMZ (Combo) groups. (B) Statistical analysis of tumor volume in Vehicle, BA-101, TMZ, and BA-101 + TMZ groups. (C) Statistical analysis of tumor volume growth comparison in Vehicle ($n = 6$), BA-101 ($n = 6$), TMZ ($n = 6$), and BA-101 + TMZ ($n = 6$) groups on different days during the treatment. (D) Kaplan–Meier plot for mice harboring U-87 MG glioblastoma xenografts treated with Vehicle ($n = 6$), BA-101 ($n = 6$), TMZ ($n = 6$), and BA-101 + TMZ ($n = 6$). Data are presented as mean ± SEM. $^{****}P < 0.0001$, $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, and ns, not significant.

volume = (length × width^2)/2. The probability of survival was determined when the tumor size was 1.5 cm in either dimension, length, or width.

Western Blots

The tissues were homogenized in a freshly prepared RIPA buffer as described previously (22). It contained 30 mM HEPES (pH 7.4), 150 mM NaCl, 1% Nonidet P-40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate, 5 mM EDTA, 1 mM Na_3VO_4, 50 mM NaF, 1 mM PMSF, and 1% protease/phosphatase inhibitors cocktail (pH 7.7). All these chemicals were purchased from Sigma-Aldrich. Homogenization was performed on ice using a Teflon pestle and a Jumbo stirrer from Thermo Fisher Scientific (Waltham, MA, USA). The homogenates underwent centrifugation at 17,000 × g for 30 min at a temperature of 4°C. The supernatant of the sample was collected, and the protein concentration was determined using the bicinchoninic acid protein assay kit provided by Sigma-Aldrich. The samples underwent polyacrylamide gel electrophoresis, after which they were transferred onto a Polyvinylidene difluoride (PVDF) membrane using

a semidry transfer method (Bio-Rad Laboratories). Nonspecific sites were effectively blocked by 5% dried skimmed milk in Tris-buffered saline with Tween 20 (TBST). The TBST solution consisted of 135 mM NaCl, 50 mM Tris, and 0.1% Tween 20, pH 7.4. This blocking process was carried out for 2 h at room temperature. PVDF membranes containing the transferred proteins were incubated overnight at 4°C on a shaker with a primary antibody. Primary antibodies used were anti-3-Ntyr [diluted 1:1000 for Western blots (WB) and 1:200 for immunofluorescence (IF)], anti-cleaved caspase 3 (diluted 1:1000), anti-cleaved PARP1 (diluted 1:1000), and anti-β-actin (diluted 1:1000). Following the exposure to primary antibodies, the membranes underwent a washing step with TBST for three times 10 min each followed by an incubation process with anti-mouse/rabbit HRP-conjugated secondary antibody for 1 h at ambient temperature. The specific binding of the protein was identified using an ECL substrate manufactured by Bio-Rad Laboratories. The bands were acquired using the Bio-Rad Chemidoc imaging system as described previously (22).

IF and Confocal Microscopy

After dissection, the tumors were directly preserved in a 4% paraformaldehyde solution for 2 days. After fixation, the tumors were gradually dehydrated with 10%, 20%, 30%, sucrose solution. Using cryostats, the 20-μm-thick tumor section was cut. The tumor sections were processed for IF. The sections were incubated in a blocking buffer followed by anti-rabbit Ki-67 (diluted 1:500), and 3-Ntyr (diluted 1:200) primary antibodies. Then, the sections were rinsed with PBS and incubated with anti-rabbit Alexa Fluor 594 (diluted 1:1000) and anti-mouse Alexa Fluor 488 (diluted 1:1000) secondary antibodies for 2 h in the dark. After the incubation with secondary antibodies, sections were washed with PBS three times and mounted on glass slides with DAPI. Images were captured at 40X using a Nikon confocal microscope.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism Software, v. 9.3 (San Diego, CA, USA). Data are presented as mean $\pm$ SEM. A two-way ANOVA followed by Tukey's multiple comparison tests was performed to analyze body weight and tumor volume on different days during the experiment. A one-way ANOVA followed by Tukey's multiple comparison test was used for the group comparisons to measure tumor volume at the end of the experiment. An unpaired *t* test was used for WB and IF. The differences between the groups were considered statistically significant at $P < 0.05$.

Discussion

Our recent study on GBM proved the involvement of nitric oxide in tumor progression and showed that NOS inhibition can prevent tumor proliferation in vitro. A study by Kruglyakov *et al.* showed that NOS inhibitors reduced GBM cell proliferation in vitro (45). The current study investigates the efficacy of NOS inhibitors in the xenograft mouse model of GBM.

Overexpression of nNOS has been reported in GBM patient samples (47). Another study also found higher nNOS activity in high-grade glioma (48). This shows the significant link between malignancy in glial tumors and NO overproduction, which can be associated with the overexpression of nNOS or its elevated activity. iNOS inhibitors have also been found to be effective in some studies for GBM treatment (49, 50).

Treatment of the xenograft mouse model of GBM with BA-103 and BA-101 in our experiments reduced tumor weight and volume, showing that NOS is implicated in cell death and tumor growth in this kind of cancer. Real-time tumor progression data showed that tumor growth was significantly inhibited by BA-103, BA-101, or the mixture of these two drugs. BA-101 appeared to be more effective in tumor volume reduction than BA-103. Combined treatment with BA-103 and BA-101 provided a more potent preventive effect on tumor growth. Further body weight measurement in all groups showed no difference. Since BA-101 displayed higher efficacy in inhibiting tumor growth than BA-103, we chose this NOS inhibitor for a dose–response study to find the most effective dose of BA-101 for treatment. BA-101 inhibited tumor growth at all doses used in this study, from 20 to 80 mg/kg. This effect was dose dependent, with the most significant inhibition of tumor progression among the doses tested being achieved at 80 mg/kg.

A nuclear protein, Ki-67, is widely used as a proliferation marker (51). Its expression correlates directly with metastasis and clinical tumor stage (52). We found that the treatment of mice with BA-101 at a dose of 80 mg/kg had lower expression of Ki-67 than the vehicle-treated group, indicating the lower proliferation of the tumor cells. Apoptosis ensures the homeostatic balance between cell proliferation and death (53–55). It represents a molecular pathway of self-destruction to eliminate the damaged or failing cells and subcellular structures and molecules and to allow their repair or replacement (56). BA-101 treatment considerably increased the cleaved caspase 3 and cleaved PARP1 levels, indicating augmented apoptosis and DNA degradation. Activation of these self-destruction processes was likely associated with the tumor volume and size growth suppression in the GBM model used in this study. Notably, the link between DNA degradation and apoptosis has been previously found, and these processes might be followed by cell detoxification and repair (57). Inhibiting nNOS can trigger apoptosis in glioblastoma cells. Reducing NO levels through nNOS inhibition disrupts survival pathways, leading to programmed cell death. This mechanism is crucial, as glioblastomas often evade apoptosis, contributing to their malignancy (58).

Further, we assessed the nitrosative stress marker 3-Ntyr levels in tumor sections. 3-Ntyr is formed by the nitration of tyrosine residues in both protein-bound and free forms by reactive peroxynitrite molecules (59). In this study, both WB and IF confirmed a reduction in 3-Ntyr levels and consequently reduced nitrosative stress in the BA-101 treatment group.

TMZ is a monofunctional DNA alkylating agent employed to treat patients with newly diagnosed GBM (60). It is a lipophilic molecule with oral administration feasibility, which can effectively cross the blood–brain barrier (61). TMZ has been a gold standard drug for GBM treatment (46). We compared the ability of BA-101 and TMZ alone and in combination to inhibit tumor growth. The reduction in tumor volume was greater in GBM mice treated with the combination of the two drugs compared to BA-101 or TMZ alone. nNOS inhibition has been shown to sensitize glioblastoma cells to chemotherapeutic agents like TMZ. Pretreatment with nNOS inhibitors decreased cell viability in glioblastoma cells exposed to TMZ (58).

The limitations of this study were that it did not include the pharmacodynamic assessments required for early-phase clinical trials to evaluate the safety and efficacy of BA-101 in patients with GBM. We consider the hurdles in clinical translation, such as variability in patient response, potential toxicity, and the need for optimized dosing regimens. This study serves as a proof of concept demonstrating the involvement of nitric oxide synthase (NOS) in GBM pathophysiology. It provides a strong foundation for future investigations to refine therapeutic strategies and advance clinical translation.

In conclusion, this study showed that NO synthesis overactivation in GBM, particularly neuronal NO production, could be an essential pathogenic factor of tumor growth. The selective nNOS inhibitor BA-101 or its combination with TMZ might be a prospective therapeutic agent for GBM treatment. Further studies are required to assess the safety and efficacy of this novel therapeutic approach in patients with GBM.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Authors Contributions

S.K.O: Animals' handling, biochemical analysis, and writing paper. M.K.T.: Animals' handling. W.B.: Animals' handling and biochemical analysis. M.K.: Contributing to the Discussion. S.G.: Data analysis. A.M.: Data analysis. M.N.: Animals' handling. I.K.: Contributing to the Discussion. H.A.: Study planning, idea conceptualization, and research supervision.

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Author Disclosures

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Internet searches for ADHD medications surged during the COVID-19 pandemic

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On January 2020, the World Health Organization (WHO) declared that Coronavirus Disease (COVID-19) had become a public health emergency of international concern (PHEIC) and was assessed as a pandemic in March 2020. For the next 2–3 years, Americans followed stay-at-home orders, and used virtual technologies, while struggling with pandemic-related stressors (1). This affected mental health (2). Attention-deficit hyperactivity disorder (ADHD) symptoms increased (3), resulting in an uptick in ADHD prescriptions (4). A shortage of Adderall was announced by the U.S. Food and Drug Administration (FDA) in October 2022. As actual prescription usage data were not available on the short time frame of the pandemic, we explored the potential of using internet searches as a proxy for real health behavior, with prevention of future shortages in mind. We used Google Trends (GT) data (5) to estimate public interest in ADHD medications during the pandemic.

GT represents analyses of Google search requests showing how popular a search term is over time. GT are normalized to make comparisons between terms: 1) each data point is divided by the total searches of the geography and time range, and 2) the result is then scaled on a range of 0–100 based on a topic's popularity compared with all topics. We find that searches for ADHD medications surged during the pandemic, and that there is a correlation between trending ADHD medication searches and real-life prescription usage.

To do this, we first performed cross-correlation analysis on GT data to identify trends spanning 20 years. Within each trend, we identified subtrends from the correlation matrix using k-medoids clustering (Supplemental Figure S1A–S1D). We label subtrends by the keyword that is most popular. We used the normalizing keyword "drugs" for comparisons with each keyword (Supplemental Tables S1F and S1G). We also performed seasonal trend analysis (Supplemental Figure S1E–S1H) for 187 disorders and 113 medication keywords. These analyses indicated increasing interest in ADHD medications.

We then noticed that ADHD disorder and medication searches surged after the onset of the COVID-19 pandemic (January 2020) (Figure 1A and B), correlating with known pandemic-associated increases in issued ADHD drug prescriptions (Chai *et al.*, 2024, *JAMA Psychiatry*) (4). As internet searches for prescription drugs may not reflect real-world prescription usage, we then compared GT ADHD drug searches with issued prescription drug rates (from the MEPS database). This showed significant correlation ($r = 0.876$, confidence interval [0.6926402–0.9531509], $p = 1.87 \times 10^{-6}$) leading up to the onset of the pandemic, as MEPS data are only available until 2021 (Figure 1C).

As GT data suggest that searches for ADHD medications correlate with prescription usage, we explored this idea further with other psychiatric drugs. We computed correlation coefficients between GT drug search data and issued prescription data (2004–2021), identifying that 47.8% of drugs have correlation greater than 0.5, and this correlation was generally greater for higher usage drugs ($r = 0.42$, Supplemental Figure S1I; Supplemental Table S1H).

Our findings match recently reported results showing that prescriptions for ADHD medications increased with the COVID-19 (4). We also found a short-term drop in GT searches for ADHD medications early in the pandemic, which matches findings from the same report (4). The long-term implications of increased public interest in and usage of ADHD medications in recent years is unclear—longitudinal data will determine whether this trend is sustained for years past the COVID-19 Public Health Emergency (PHE) which ended in May 2023.

This study has several limitations: 1)data were not representative of the general population, potentially excluding individuals with limited online literacy and internet access—other internet usage demographics could bias results as well; 2)though internet searches correlate with actual prescription use in the context of this study, this correlation may not hold for different health issues or for different times or places—a factor that could cause such a dissociation include media coverage of drugs; and 3) ADHD diagnoses and medication prescriptions moved heavily online during the pandemic, which may have increased their rates.

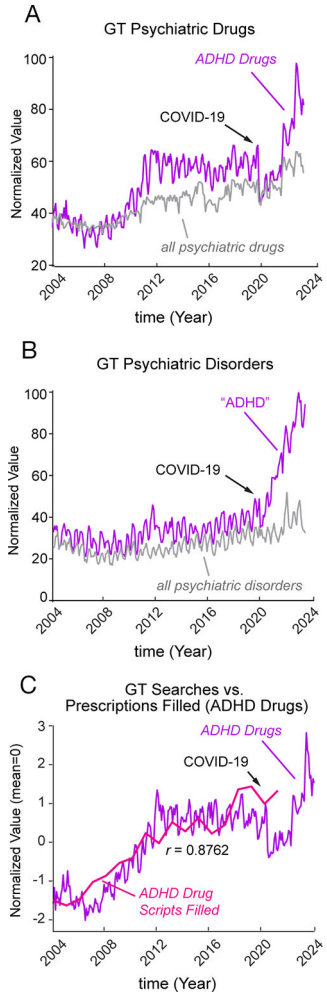

Figure 1. Public interest in ADHD medications surges during the COVID-19 pandemic. (A) GT search popularity for ADHD medications (purple) (key terms amphetamine+adderall, methylphenidate+ritalin, dextroamphetamine+dexedrine, lisdexamfetamine+vyvanse, dexmethylphenidate+focalin, atomoxetine+strattera, clonidine+kapvay, guanfacine+intuniv) compared with search terms for all psychiatric medications (gray). (B) GT search rates for "ADHD" compared with search rates for all psychiatric disorders. (C) GT ADHD drug searches (key terms amphetamine+adderall, dextroamphetamine+dexedrine, and lisdexamfetamine+vyvanse) compared with drug prescription issuance rates from the MEPS (key terms ADDERALL*, *AMPH*, VYVANSE*, *AMFET*, * indicate free characters), shows correlation $r = 0.8762$ (2004–2021).

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Going forward, public health departments and drug manufacturers may explore GT search data as a proxy for prescription usage during rapidly changing public health emergencies in which real prescription usage data are not yet available. For this approach to be effective on a wide range of health topics, additional studies will need to scale-up and refine the approach. A working relationship between public health departments, drug manufacturers, and industry partners who own the data, will be essential for making real-time predictions about the public's prescription usage. This partnership could detect the timing and geographical patterns of new drug interest changes, and perhaps even warn of fraudulent overprescribing.

In conclusion, GT may provide a potential method for public and private health officials to respond to rapidly changing public health situations, allowing pharmaceutical companies to accurately meet demands for prescription drug usage.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

SFG and KGJ designed, analyzed the data and wrote the manuscript. XX helped to oversee the project.

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Therapeutic apheresis: A promising method to remove microplastics?

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Microplastics and nanoplastics have emerged as a major and growing health concern, with recent data revealing alarming levels of human exposure and contamination. Thus, there is a clear and urgent need for an effective method to remove microplastics and nanoplastics from the human body. Here, we provide the first evidence that extracorporeal apheresis, a therapeutic technique established around the world, may have the potential to achieve this goal.

Microplastics (1 μm–5 mm) and nanoplastics (<1 μm) (MNPs) are small plastic particles originating from commercial production, such as cosmetics and medical drugs and from the degradation of large plastic waste. MNPs are virtually omnipresent and only lately the concerning magnitude and health dimension of this environmental threat is becoming evident (1, 2).

Due to current methodological limitations, we prefer to speak about MNPS or MNP-like structures, which may consist of MNPs combined with other molecules, such as proteins. It is crucial to emphasize that correct sampling and storage are extremely sensitive steps in the workflow, as contamination occurs instantly (2, 3). To ensure the reliability of findings, strict quality standards should always be applied. Given these limitations, recent studies reporting the presence of microplastics in numerous tissues, including the lung, heart, gut, liver, brain, and metabolically active tissues (4, 5), should be interpreted with some caution. Nonetheless, growing evidence suggest that MNPs may contribute to the development and progression of various conditions, including cardiovascular and metabolic diseases, infertility, cancer, and even neurodegenerative disorders such as dementia (5, 6). Moreover, it has been proposed that MNPs engulfed in adrenal tissue may alter steroidogenesis and cortisol levels (7, 8), and that perturbations in stress regulation may contribute to symptoms of chronic fatigue following viral infections. Additionally, MNPs may facilitate the transport of infectious particles into tissues and cellular compartments (9, 10), though further research is needed to confirm these mechanisms.

Given the ubiquitous presence of MNPs in the environment, completely avoiding exposure is unrealistic. While some initiatives promote a global strategy to reduce the intake of MNPs, there remains a critical need for an effective method to remove them from the human body. Therefore, our group recently suggested that extracorporeal therapeutic apheresis could be used to remove environmental factors (11). Apheresis is an extracorporeal technique used to selectively remove specific blood components, such as particular cells or plasma constituents (Figure 1A). Previously, we and others demonstrated that up to 70% of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), including some with long COVID, reported a significant improvement in their symptoms following extracorporeal apheresis (12–15).

An astonishing rise in patients with ME/CFS has been linked to the increasing levels of environmental airborne particle matter 10 μm or less in diameter (16). In the current study, we have investigated whether therapeutic apheresis can remove MNP-like particles from

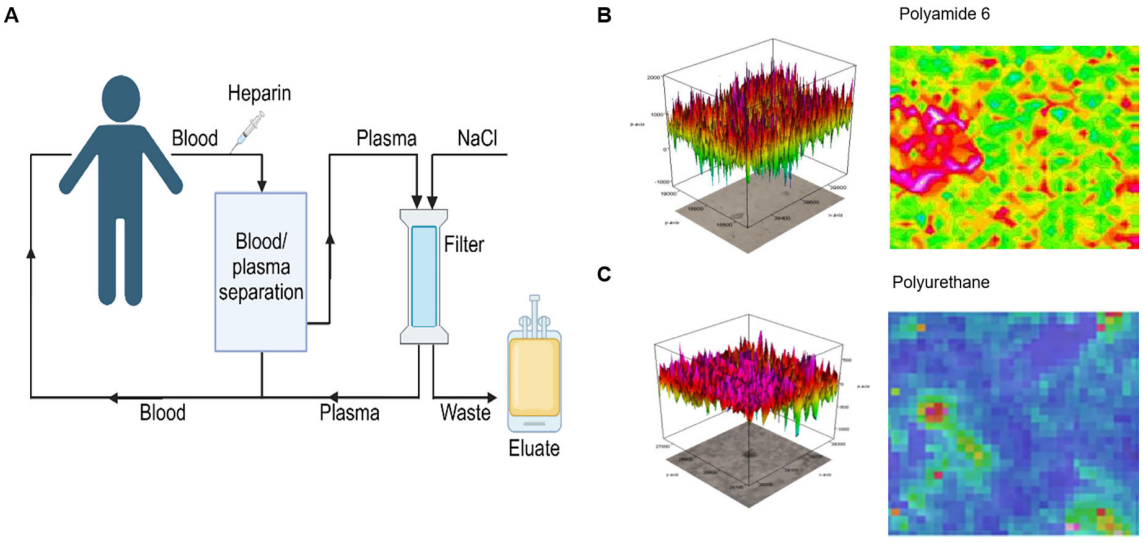

Figure 1. Extracorporeal therapeutic apheresis removes microplastic- and nanoplastic-like particles from human blood. (A) Schematics of an extracorporeal apheresis system. First blood is drawn from a large vein and processed through an apheresis machine. Then a porous membrane is used to separate blood cells from plasma. The plasma is processed through specific filters for removal of different blood components such as lipids or autoantibodies. After removal of the targeted component, the remaining blood components are reinfused into the patient through a second venous access. The components removed from the plasma, potentially including microplastics and nanoplastics, will be contained in the eluate. Created with BioRender.com. (B and C) Two examples from 21 patient samples demonstrating microplastics in the concentrated eluate removed from the patients' blood, measured by ATR-FT-IR. The full IR spectra, followed by analysis of individual spots, showed a 67.5% match with polyamide 6 (B) and a 35.3% match with polyurethane (PUR-WS) (C).

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the human body. Twenty-one patients with a confirmed diagnosis of ME/CFS related to a postinfectious syndrome, received at least two cycles of therapeutic apheresis with double filtration (INUSpheresis) (Figure 1A). The concentrated eluate sequestered from the blood circulation during apheresis was analyzed for MNP-like particles after each treatment using attenuated total reflection Fourier transform infrared (ATR-FT-IR) spectroscopy (for further details see *supporting online material*). The analysis of the patient eluates showed that 14 different substances or mixtures of substances could be detected only in the eluates from these patients with resemblance to for example polyamide 6 and a polyurethane, PUR-WS (Figure 1B and C). Polyamide 6, also known as nylon 6, is a synthetic polymer primarily produced as a fiber rather than a particle. For specialized applications, electrospun fibers are manufactured with diameters below 100 nm, which may explain why we can detect particles in eluates that were double filtered (blood separator and TKM58 apheresis filter) with pore sizes of $\leq$ 200 nm. Of note, this analysis does not quantitatively measure MNPs; it only determines whether MNP-like particles are present or not. The MNP-like particles found in eluates from patient samples were not present in any samples from the filter prerinse process (Supplementary Figure S1), indicating that they can only be attributed to the patient eluates. However, as ATR-FT-IR spectroscopy detects polyamide bonds, it should be noted that these could also originate partly from proteins.

As mentioned above, there is increasing evidence that MNPs can be associated with a number of health problems (5–8). However, the long-term effects and specific mechanisms still need to be further elucidated. Different analytical methods have been developed to identify and characterize MNPs, each with distinct capabilities and limitations in relation to morphology, chemical composition, and quantity (17). Until now, no methods have been reported for removing MNPs from the human body. In this study, we demonstrate for the first time that extracorporeal therapeutic apheresis might have this capability. However, larger patient cohorts and quantitative analyses, such as pyrolysis gas chromatography mass spectrometry, are required to confirm the effective removal of MNPs through therapeutic apheresis. This should include measuring MNP levels in plasma samples before and after apheresis, as well as in eluates, across multiple cycles. Such analyses will help determine particle removal from blood and tissues and assess correlations with symptom improvement in conditions like ME/CFS. We recommend a comprehensive study on the removal of MNPs using various filter systems with different pore sizes to develop strategies for both preventing uptake and facilitating detoxification of accumulated particles.

Ethics

All participants in the study have provided written consent.

Author Disclosures

G.P., R.S., and K.V.-B. work at INUS Medical Center AG in Cham, offering therapeutic apheresis as a treatment for conditions such as chronic fatigue.

Data Availability

The datasets generated during and/or analyzed during the current study are included in this published article (and its supplementary information files) or available from the corresponding author.

Author Contributions

RS and KVB designed research; GP, RS, and KVB collected the clinical data; TG, DK, AEA, and LP performed research. SRB, MY, WK, KVB, JL, and CS analyzed data. CS and SRB wrote the initial draft of the paper; All authors read and approved the manuscript.

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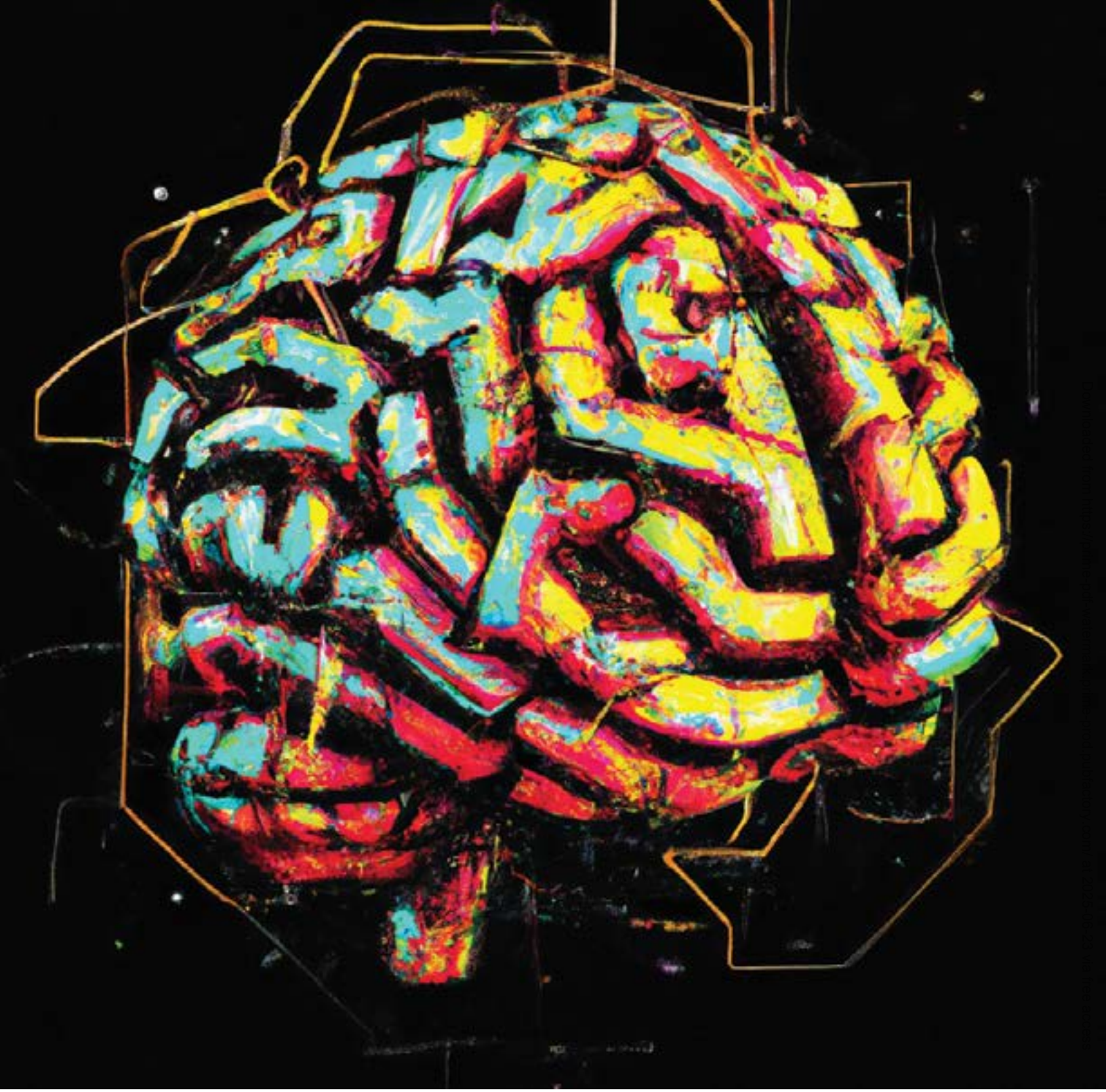

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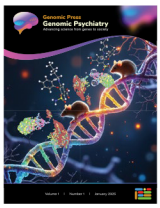

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