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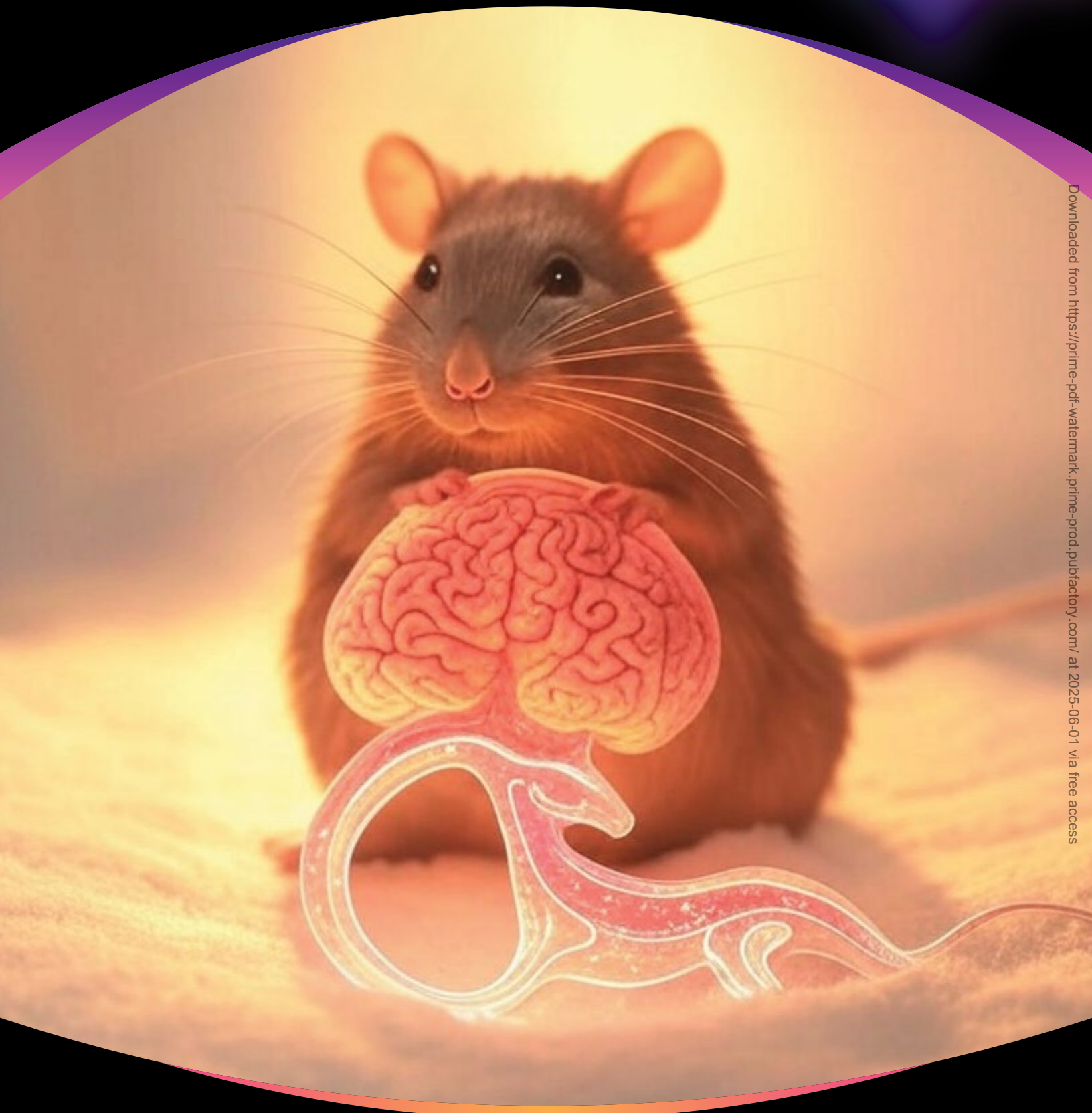

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Cover Art

A conceptual visualization depicting the impact of maternal immune activation on hippocampal neuron development. A laboratory rat is shown holding a transparent model of a brain with visible neural pathways, symbolizing the relationship between maternal infection during pregnancy and altered neuronal excitability in offspring. The warm amber tones of the rat contrast with the translucent pink-hued brain model, representing the delicate balance of neurotransmission affected by prenatal immune challenges. The ethereal glow extending from the brain highlights the glutamatergic pathways particularly vulnerable to maternal immune activation, with connections illustrated flowing into crucial hippocampal regions. This image reflects the findings presented in "Maternal immune activation impairs hippocampal pyramidal neuron excitability in newborn rat offspring: Implications for neurodevelopmental disorders" by Lucia Moravcikova et al. on pages 46-52 in this issue.

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EDITORIAL

Medication-induced sterol disruption: An overlooked threat to brain development and public health

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Scientific progress often demands that we revisit comfortable assumptions. Occasionally, new data do more than inform—they provoke. The article by Korade and Mirnics in this issue of *Brain Medicine* is a rare and necessary provocation (1). It unveils a silent hazard: that a broad array of widely prescribed drugs, developed and approved for disparate conditions, may converge on a shared off-target toxicity. These medications disrupt sterol biosynthesis—an essential metabolic process underpinning neural development—and do so in ways that mirror the biochemical footprint of devastating genetic syndromes.

Cholesterol, a molecule that has captivated scientific inquiry for generations, stands among the most intensely studied compounds in history—as evidenced by the thirteen Nobel laureates whose distinguished careers were significantly devoted to unraveling its mysteries (2).

While clinical discourse often portrays cholesterol as a cardiovascular villain, its role in the brain reveals a profoundly different narrative. Within this delicate neural landscape, cholesterol emerges not as an adversary but as an indispensable element—a fundamental cornerstone of cerebral architecture without which life itself could not exist. The brain contains a disproportionate 25% of the body's cholesterol, despite accounting for only 2% of total mass (3). This is not incidental—it is the molecular scaffolding upon which brain architecture and connectivity are built. Cholesterol is central to synapse formation, axonal guidance, dendritic arborization, and myelin integrity. Cholesterol and sphingolipids, embedded within membrane raft microdomains, serve as critical signaling molecules that facilitate neuronal differentiation and synaptogenesis, making their proper metabolism essential for maintaining brain function and preventing neurological and neurodegenerative diseases (4). It is actually fascinating that two decades ago there was a race to identify a glia-derived factor that strongly promotes synapse development in cultures of purified CNS neurons. Mauch et al published a paper in Science in 2001 identifying this factor as cholesterol complexed to apolipoprotein E-containing lipoproteins (5). It is therefore not surprising that cholesterol homeostasis is so critical that the brain maintains an autonomous cholesterol economy, isolated by the blood-brain barrier from systemic fluctuations.

From early gestation to late adulthood, this self-contained biosynthetic machinery sustains cognitive and neural function. Genetic disruptions of this pathway—such as in Smith-Lemli-Opitz Syndrome (SLOS), lathosterolosis, desmosterolosis, CDPX2, CHILD syndrome, SC4MOL deficiency, and HEM dysplasia, all caused by pathogenic variants in critical sterol biosynthesis genes—produce catastrophic developmental outcomes (6, 7). This has long served as a warning: perturbing sterol homeostasis in the developing brain is not compatible with health.

Korade and Mirnics have a strong record in this area (8) and what their work has highlighted is profoundly unsettling. Over 30 FDA-approved drugs—among them, psychiatric mainstays such as aripiprazole, trazodone, haloperidol, and cariprazine—have been shown to inhibit DHCR7. This inhibition raises the levels of 7-dehydrocholesterol (7-DHC), suppresses cholesterol synthesis, and generates a sterol profile indistinguishable from that seen in congenital metabolic disorders. This is not a hypothetical concern—it is empirically validated in cell lines, rodent models, and human blood samples. Notably, a comprehensive, systemic review by Bolland and Tatonetti investigated the fetal outcomes following prenatal exposure to DHCR7 modulators, and conceded that *"first-trimester exposure to DHCR7 inhibitors resulted in outcomes similar to those of known teratogens"* in humans (9).

Even more alarming is the fact that 7-DHC is not inert. It is biochemically volatile—the most oxidizable lipid known in humans with a reactivity 200 times greater than cholesterol. Its accumulation results in the formation of toxic oxysterols such as DHCEO, which impair neurite outgrowth, alter cellular morphology, and damage the fundamental architecture of neuronal connectivity (7, 10, 11). These are not esoteric molecular details. These are mechanisms of harm.

The scenario becomes even more concerning when one considers the effect of polypharmacy. In experimental systems, combinations of two or more DHCR7-inhibiting drugs elevate 7-DHC to levels more than 15 times above control (12, 13). Pregnant women taking multiple such medications exhibited the highest concentrations of 7-DHC in their blood. These effects are not additive—they are often synergistic. And they are happening under the radar of our regulatory systems.

Here, we encounter a pivotal failure in modern pharmacology: regulatory drug approval is based almost exclusively on single-agent safety data, despite the clinical reality that it has become increasingly common for patients to rely on the use of multiple prescription medications (14, 15). Preclinical toxicology, clinical trials, post-marketing surveillance—all assume that medications will be taken in isolation. But that assumption collapses in real-world clinical settings. Most patients—especially those with chronic psychiatric or medical conditions—take multiple drugs simultaneously. Yet these combinations are typically not tested together, not even in animals, let alone in pregnant women or infants. This is a blind spot of breathtaking scale.

What Korade and Mirnics reveal is especially disturbing in this context. If individual drugs can mimic a metabolic disorder, what are we to make of their interactions? We are prescribing molecular cocktails with no empirical knowledge of how they alter developmental neurochemistry. The combinations that are most common in clinical practice are also the least studied. This is not an oversight. It is a systemic design flaw in how we evaluate drug safety (see Fig. 1).

And the vulnerable populations are not hypothetical. At least 1–3% of the general population carry single-allele DHCR7 mutations (16). These individuals are typically asymptomatic, but they live on the edge of sterol balance. A single prescription can tip that balance. Two or more may send them into a biochemical state that resembles SLOS. Neither the clinician nor the patient would ever know.

Moreover, the developmental windows of vulnerability extend well beyond gestation. Myelination, glial proliferation, synaptic pruning, and hormonal shifts occur through infancy, childhood, and adolescence (17). These stages are marked by high demand for sterol-derived signaling and membrane components (18). The sterol-disrupting effects of drugs administered during these periods may manifest not as malformations

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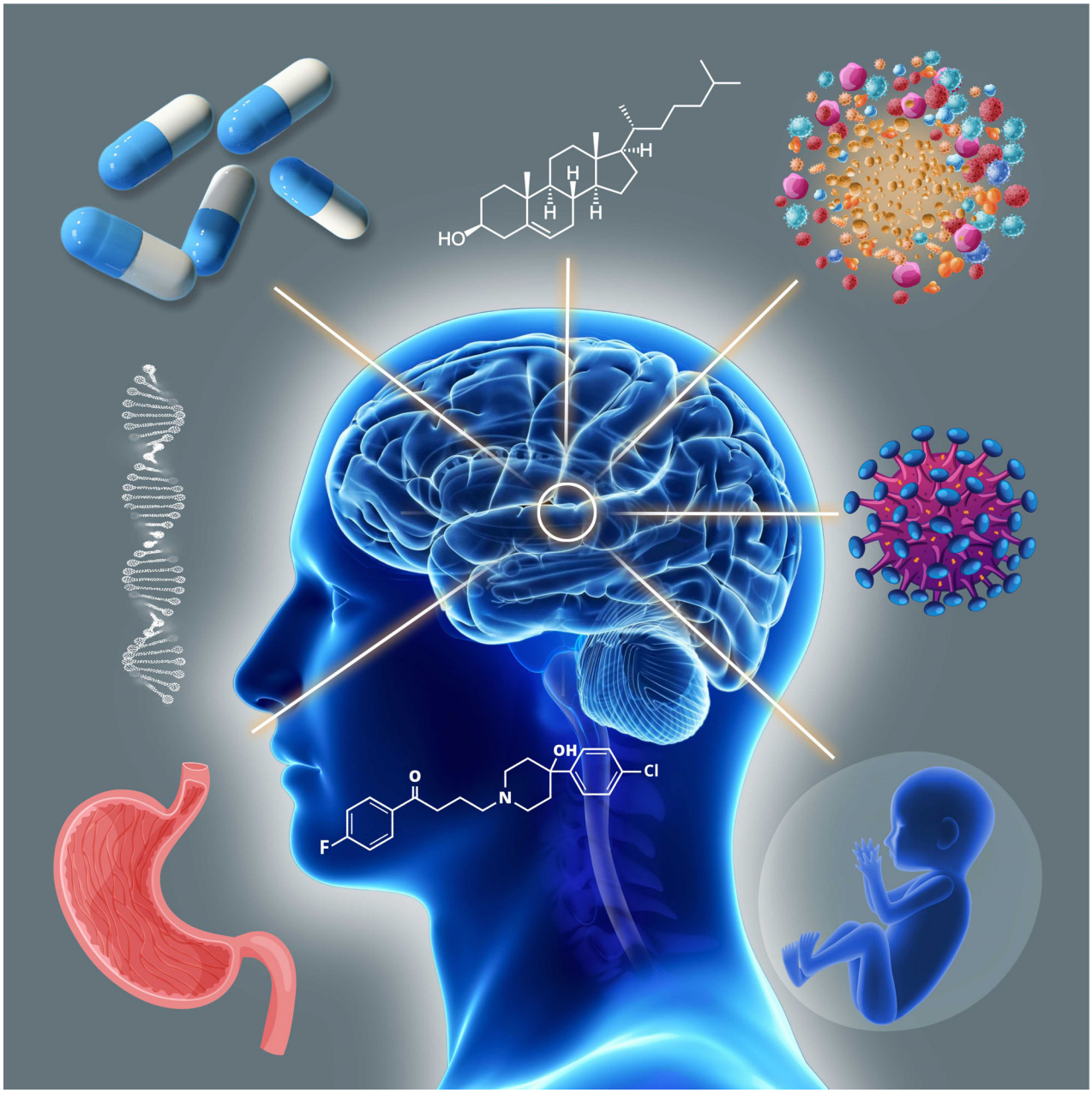

Figure 1. Medication-induced disruption of sterol biosynthesis poses significant risks to brain development and function. At the top center of this schematic lies the cholesterol molecule—an anchor of neurobiological integrity—flanked by the structure of haloperidol embedded within the brain, exemplifying one of over 30 FDA-approved compounds known to inhibit DHCR7. These agents, many of which are orally administered and processed through the gastrointestinal–hepatic axis, initiate biochemical disruptions at the level of first-pass metabolism, altering sterol homeostasis before the compounds even reach the central nervous system. The result: accumulation of toxic precursors such as 7-dehydrocholesterol (7-DHC) and their conversion into highly reactive oxysterols (top right), with well-established neurotoxic potential. On the left, a DNA strand signals genetic vulnerability, which can amplify these pathological cascades—particularly during periods of neurodevelopmental sensitivity (lower right). The diverse array of medications (pills, upper left) underscores the wide pharmacologic footprint of this off-target effect, raising serious concerns about additive or synergistic toxicity in the context of polypharmacy. Taken together, this mechanism—once overlooked—demands urgent attention as a pressing public health concern, particularly for developing brains and genetically susceptible populations.

but as subtler, chronic, functional impairments: cognitive delay, emotional dysregulation, behavioral disturbance. We are not tracking these outcomes. We are not even looking.

The implications are immense. The pharmaceutical industry must immediately incorporate sterol biosynthesis screening into all developmental safety assessments. Regulatory agencies must abandon the fiction of monotherapy testing and require at least some modeling of common drug combinations. Clinical trial designs must evolve to reflect the messy reality of modern medicine. And post-marketing surveillance must include not only short-term adverse events but also long-term developmental and behavioral endpoints.

Clinicians, too, must respond with heightened vigilance. Genetic testing for DHCR7 pathogenic variants (and other post-lanosterol biosynthesis enzymes) should be considered in women of childbearing age who require medications known to disrupt sterol synthesis. Polypharmacy involving such drugs should be avoided during pregnancy

whenever possible. Patient counseling must include discussions of these risks—especially in psychiatric care, where these medications are often initiated early and continued long-term.

Korade and Mirnics are not offering a mere caution. They are challenging the very architecture of how we think about drug safety. The problem they highlight is not that a few drugs have an unfortunate side effect. It is that our entire system of medication evaluation ignores the complexities of developmental biology, genetic susceptibility, and real-world prescribing patterns.

We must no longer regard sterol biosynthesis as an obscure metabolic pathway. It is a central axis of brain development. And the disruption of that axis—whether by mutation, medication, or both—has consequences that are profound, irreversible, and avoidable. Despite decades of pharmaceutical development, we lack a comprehensive catalogue of FDA-approved medications with sterol-inhibiting side effects—a critical knowledge gap that may obscure iatrogenic disruptions of this essential pathway.

This is a call to action. Not someday. Now.

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INNOVATORS & IDEAS: RISING STAR

Munir Gunes Kutlu: Exploring the neural mechanisms of learning and social behaviors – A scientist's journey and perspective

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Keywords: Learning and memory, social cognition, dopamine, striatum, computational modeling, learning theory

Dr. Munir "Gunes" Kutlu, Assistant Professor at the Center for Substance Abuse Research (CSAR) and the Department of Neural Sciences at Temple University Lewis Katz School of Medicine, investigates the neural mechanisms underlying associative learning, mainly focusing on reward, fear, and social interaction. Drawing from his computational neuroscience training at Duke University and postdoctoral work at Temple and Vanderbilt Universities, Dr. Kutlu combines systems neuroscience, computational approaches, and behavioral analysis to understand how our brains process environmental associations and how these processes can become maladaptive in disease states. His laboratory, dedicated to "bridging the brain-behavior gap," fosters a collaborative environment that nurtures the next generation of neuroscientists while pursuing innovative neural circuit analysis approaches in reward and aversive learning contexts. In this Genomic Press interview, Dr. Kutlu shares his insights on these fascinating aspects of behavioral neuroscience and his laboratory's mission to advance our understanding of neural circuit function in health and disease.

Part 1: Munir Gunes Kutlu – 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 grew up with a natural curiosity about how things work, but my true passion for science was ignited during my undergraduate studies when I took my first neuroscience course. There, I was fascinated by the complexities of the brain and the potential to understand behaviors through neural mechanisms. Each step of my journey, from obtaining my Ph.D. through my postdoctoral training to starting my own lab, has been fueled by a desire to uncover how the brain drives behavior. I conducted my first research project on understanding learning mechanisms in humans. This experience showed me the power of combining behavioral analysis with computational modeling, shaping my future research path toward understanding the neural circuits underlying learning and memory.

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

I grew up in Istanbul, Turkiye, where I received my bachelor's degree in psychology at Bilgi University. At Bilgi, I conducted a thesis project on the mathematical models of associative learning as an undergraduate. Following my interest in the theory, I did my Ph.D. at Duke University under my mentor, Dr. Nestor Schmajuk, studying the theory and computational models of learning and memory. The second pivotal moment in my career was my postdoctoral training under Dr. Erin Calipari at Vanderbilt University, where I was trained in in-vivo neural recording techniques, which allowed me to examine the neural circuits supporting the learning and memory mechanisms I previously studied at the theoretical and behavioral levels. As a result, in my lab at Temple University Lewis Katz School of Medicine, I study learning and memory as well as social behaviors in several different analytical levels, such as from theory to behavior and circuit biology.

Figure 1. Munir Gunes Kutlu, PhD, Temple University Lewis Katz School of Medicine, USA.

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

My fascination with the brain's ability to encode information began during my undergraduate studies when I was introduced to associative learning models like the Rescorla-Wagner and Pearce-Hall models. Exploring how these models predict learning through associations between stimuli and responses sparked my curiosity about the neural mechanisms underlying these processes. I liked the idea that complex behaviors could be

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understood through relatively simple mathematical frameworks, which led me to delve deeper into how the brain implements these computational principles. This early exposure to associative learning theories laid the foundation for my research, which focuses on understanding how the brain encodes, processes, and retains information, especially in the context of reward-based learning and social interactions. It was a defining moment that set the course for my future work in neuroscience.

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

The primary impact I hope to achieve in my field is to uncover how our brains perform fundamental calculations about our surroundings, particularly in making decisions about rewards and dangers. My research aims to decode the neural processes that enable us to assess our environment, predict outcomes, and make adaptive decisions. By focusing on associative learning and neural encoding mechanisms, I strive to understand how the brain transforms sensory inputs into meaningful predictions that guide behavior. Ultimately, my goal is to reveal how neural circuits integrate information to evaluate risks and rewards, shedding light on the underpinnings of decision-making processes. This research has the potential to inform our understanding of mental health conditions where these computations go awry, such as anxiety, addiction, and social dysfunction, paving the way for new therapeutic strategies.

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

My current scholarly focus centers on associative learning, specifically how memories are encoded and maintained in the brain and how these processes influence decision-making when interacting with our environments and others in social settings. Our primary focus is to discover where fundamental learning and memory computations such as novelty, prediction error, saliency, and attention are encoded in the brain. We have published a series of manuscripts examining the role of dopamine release in the striatum and its role in encoding prediction error and saliency during associative learning. Challenging the current dogma of dopaminergic information encoding, we found that dopamine release in the nucleus accumbens core signals perceived saliency, an associative learning term for how salient external stimuli are perceived independent of their physical saliency. Similarly, we identified valence-free information encoding properties of D1 and D2 medium spiny neurons in the nucleus accumbens. I continue this line of work in my lab and expand it to other neurotransmitter systems, such as acetylcholine and single-cell neural ensembles.

I am also particularly interested in understanding how neural circuits, including those in the striatum, adapt to experiences of social competition and how these adaptations influence behavior and decision-making. Additionally, I am exploring the role of drugs of abuse in altering these processes. Stimulants such as cocaine and nicotine can profoundly affect how memories are formed and how social decisions are made, often leading to maladaptive behaviors that impair social functioning. By examining how these substances disrupt neural plasticity and reward systems, my research aims to uncover the mechanisms that underlie addiction and its impact on social cognition. I study how social hierarchies are established through behavioral paradigms and how environmental and pharmacological factors can modify them. By combining these behavioral tools with advanced neurotechnologies, such as fiber photometry for real-time monitoring of neurotransmitter release, I aim to gain a deeper understanding of how associative natural and drug-induced changes influence learning and memory processes in brain function. This research has broad implications for understanding addiction, competition, and the neural basis of social behavior.

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 studies and postdoctoral experiences, I developed a solid commitment to rigorously analyzing data from various perspectives and analytical levels before reaching conclusions. This approach ensures that our findings are both reliable and robust while fostering a deeper understanding of the questions we seek to answer. In my research environment, we challenge ourselves not to accept current dogmas about the brain and behavior at face value. Instead, we critically evaluate these prevailing ideas through the lens of our data, questioning assumptions and exploring alternative interpretations. This mindset encourages innovation and helps us uncover insights that may disrupt conventional thinking. By integrating rigorous analysis with a willingness to challenge established norms, we strive to contribute to a more nuanced and accurate understanding of the brain and its relationship to behavior.

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?

Free thinking is the cornerstone of all scientific progress. The ability to question, challenge the status quo, and push boundaries drives innovation and leads to breakthroughs. However, for science to truly thrive, we must ensure that free thinking is not confined to a select group but is accessible to individuals across borders, cultural identities, and socioeconomic boundaries. Transformative scrutiny within the scientific community is needed to dismantle barriers that limit participation. There are untapped perspectives and ideas in regions and communities that need access to resources or opportunities to engage in scientific discourse. By creating an environment where merit and curiosity are the driving forces, we empower individuals to contribute their unique insights and creativity. This diversity of thought enriches the scientific process and ensures that the progress we achieve benefits all of humanity, not just a privileged few.

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

What I most enjoy in my role as an academic and researcher is the freedom to be creative, to think deeply, and to ask meaningful questions. The academic environment provides a unique space where curiosity is celebrated, allowing us to explore novel ideas, challenge established perspectives, and pursue questions that inspire innovative approaches. That said, this freedom is not without its challenges. Funding concerns can sometimes hinder the extent to which bold, exploratory science can be pursued. The need to align research with funding priorities or to secure resources often imposes certain constraints on creative exploration. However, these challenges also inspire resilience and ingenuity, driving me to find innovative ways to balance creativity with practicality. Even within these limitations, the ability to ask questions and seek answers remains one of the most rewarding aspects of my work, fueling my passion for discovery and progress.

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

Outside of my professional life, I enjoy engaging in physical activities that challenge both my body and mind, such as rock climbing, as shown in Figure 2. It is a rewarding way to stay active and healthy while pushing myself to overcome obstacles. I am also a big fan of Turkish soccer, and as a proud supporter of Galatasaray, I love following their games and cheering them on. Above all, the most fulfilling way I spend my time is with my kids and family. Whether it is playing, exploring, or simply relaxing together, these moments bring me the greatest joy and help keep me grounded. My family is my biggest source of happiness and inspiration, and they make every day meaningful.

Figure 2. Gunes Kutlu scaling rock faces in Utah's dramatic landscape. Beyond the laboratory, he finds both challenge and clarity in climbing – a pursuit that demands the same focus and determination he brings to his neuroscience research.

Part 2: Munir Gunes Kutlu – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Knowing my kids are happy and healthy.

What is your greatest fear?
My greatest fear is facing a situation where, no matter what I do, I cannot prevent a negative outcome for my loved ones.

Which living person do you most admire?
I do not have a single person I admire the most, but rather a multitude of individuals across different fields who inspire me deeply. In science, I greatly admire those who challenge established dogmas and push the boundaries of conventional thinking, driving innovation and progress. In sports, I respect athletes who demonstrate exceptional talent, resilience, and dedication to their craft. These individuals inspire me in different ways, reminding me of the power of perseverance and boldness in achieving meaningful change.

What is your greatest extravagance?
My greatest extravagance is traveling. I deeply value the experiences and memories that come from exploring new places, immersing myself in different cultures, and broadening my perspective on the world. It is an indulgence that enriches both my personal and professional life.

What are you most proud of?
I am most proud of my family. Reflecting on my journey, I see we have come a long way from very modest beginnings, grappling with financial

[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.

challenges and an uncertain future. To have built a stable life and career that enables me to support and provide for my family is a profoundly cherished achievement. Their love and presence are my most significant source of pride and fulfillment.

What is your greatest regret?
There are certainly moments in my life where I could have made more informed decisions, but I strive to live without dwelling on past actions. Instead, I focus on learning from those experiences and moving forward with a mindset of growth and self-improvement.

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

What is the trait you most dislike in people?
The trait I most dislike in people is a lack of ambition or a sense of purpose—when someone has no goal or pursuit to strive for.

What do you consider the most overrated virtue?
In my opinion, blind obedience or unquestioning compliance is the most overrated virtue. While discipline and respect for authority have their place, progress is driven by curiosity, critical thinking, and the courage to challenge established norms. With questioning and reevaluating, true growth and innovation become more accessible.

What is your favorite occupation (or activity)?
Watching soccer or "futbol" as we call it in Turkish.

Where would you most like to live?
Somewhere on the coast of the Mediterranean Sea.

What is your most treasured possession?
As a physical object, my most treasured possession is a Galatasaray jersey signed by the entire team. Beyond the jersey, however, my most cherished "possessions" are the memories and experiences I have shared with my family, which bring joy and meaning to my life daily.

When and where were you happiest? And why were so happy then?
Right now, I am happiest. Having my kids around me and spending time with them fills my life with joy and meaning. I know that in 10–20 years, I will look back on these days with fondness and nostalgia, cherishing the moments we share now. Knowing how precious and fleeting it is is a fantastic time in life that I sincerely appreciate.

What is your current state of mind?
My current state of mind is focused and determined. I am fully dedicated to building my lab and fostering its growth. This phase is exciting and challenging, filled with opportunities to lay the foundation for meaningful research and to create a collaborative environment that supports discovery and innovation.

What is your most marked characteristic?
My most marked characteristic is my determination—when I focus on a problem, I do not let it go until I have found a solution. This persistence drives me to dig deeper, explore every angle, and keep pushing forward, no matter how challenging the task may be.

Among your talents, which one(s) give(s) you a competitive edge?
Among my talents, my grit and determination give me a competitive edge. Once I set my sights on a goal, I am relentless in my pursuit, overcoming obstacles and staying focused until I achieve it. This resilience allows me to navigate challenges and maintain momentum, even in the face of adversity.

What do you consider your greatest achievement?
In my career, my greatest achievement is establishing my lab at a top research institution, where I can contribute to advancing science and mentoring the next generation of researchers. In my personal life, my greatest achievement is undoubtedly my family—they are my source of joy, support, and inspiration, and nothing brings me greater fulfillment than being with them.

If you could change one thing about yourself, what would it be?
If I could change one thing about myself, it would be to worry less about imagined problems. Sometimes, I overthink situations that may never happen. I want to focus more on the present and tackle challenges as they come. This is something I am actively working on to improve.

What do you most value in your friends?
Loyalty.

Who are your favorite writers?
During my teenage years, Amin Maalouf was my favorite author. I read all of his books and was captivated by his ability to seamlessly weave history with fiction. These days, I lean more toward non-fiction. While I do not have a single favorite author, I enjoy reading works by Niall Ferguson, Malcolm Gladwell, and Yuval Noah Harari, all of whom offer fascinating insights into history, society, and human behavior.

Who are your heroes of fiction?
I do not believe in heroes, especially fictional ones.

Who are your heroes in real life?
While I am skeptical of the hero concept, I resonate deeply with Albert Camus and his worldview.

What aphorism or motto best encapsulates your life philosophy?
"The struggle itself towards the heights is enough to fill a man's heart. One must imagine Sisyphus happy." — Albert Camus, *The Myth of Sisyphus and Other Essays*.

Philadelphia, Pennsylvania, USA
30 November 2024

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INNOVATORS & IDEAS: RISING STAR

Alessandra Borsini: What neuroinflammation has to do with depression and how nutrition can play a beneficial role

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Keywords: depression, neuroinflammation, neurogenesis, nutrition, mind-body interface

Alessandra Borsini is a Lecturer in Psychoneuroimmunology at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London. Her research interest focuses on the role of inflammation and stress on brain neurogenic alterations, particularly in the context of neuropsychiatric and neurodegenerative disorders, and on the ability of psychotropic, anti-inflammatory, and nutrition-based treatments to prevent such alterations. She has been a member of the Medical Research Council (MRC) Immunopsychiatry Consortium, the AMBROSIAC ERA-NET/MRC Consortium, and the European College of Neuropsychopharmacology (ECNP) Immuno-Neuropsychiatry Network Core Group. She has received various awards, including the Psychoneuroimmunology Award from the Psychoneuroimmunology Research Society (PNIRs) and the Preclinical Psychopharmacology Award from the British Association for Psychopharmacology (BAP). As of April 2024, Dr Borsini has published over 50 papers, with a current H-index of 25, and has been the recipient of both national and international research grants from the National Institute for Health and Care Research (NIHR), Wellcome Trust, MRC, European Commission and Rosetrees Trust. She is part of the Editorial Board of several journals, including *Brain, Behavior, and, Immunity*, *Frontiers in Neuroscience*, and *Frontiers in Psychiatry*. She is also the programme leader for the new MSc in Psychology and Neuroscience of Mind-Body Interface launching this September 2024 at the IoPPN. Dr Borsini is passionate about public engagement. To discuss her research or topics broadly related to mental health, she has made multiple media appearances in newspapers, including *The Sunday Times*, *The Guardian*, and *The Independent*, and radio and TV programmes, such as *BBC Radio 4 Today*, *BBC Radio 4 All in the Mind*, and *BBC One Health: Truth or Scare*. Dr Borsini graciously answered the Genomic Press Interview, providing our readers with reflections on her personal and professional journey.

Part 1: Alessandra Borsini – 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 found the possibility of becoming one day a researcher and neuroscientist fascinating. I have a strong sense of curiosity, which led me to move from my little town in Italy to London and to apply for what at that time was considered a very novel BSc course in Psychology and Neuroscience. Studying the neuroscience of the brain and conducting laboratory experiments already during my degree, as well as being immersed in such an international academic and research environment, all contributed to increasing my passion for a career in neuroscience research.

Figure 1. Alessandra Borsini, PhD, King's College London, UK.

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 finishing my undergraduate degree, I have had a very continuous career path. I had the opportunity to meet Carmine M. Pariante at the IoPPN, King's College London, and to do a PhD under his supervision. Since then, I have had the great fortune to have him as my mentor and friend. As soon as I finished my PhD, I was awarded a Fellowship from the NIHR, which allowed me to continue my academic career at the IoPPN. I was lucky to find a fantastic community of friends and scientists, so I decided to continue my research there even after my Fellowship ended. Even though I am now a Lecturer in Psychoneuroimmunology at the IoPPN, and have been at the Institute for many years, I feel like I am still at the beginning of my journey.

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

I have always been fascinated by inflammation – its complexity, ability to change, adapt, and interact with multiple systems, and affect simultaneously both the brain and the body. At the same time, my parallel interest in the intricate complexity of specific brain processes, such as neurogenesis

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and neuroplasticity, brought me closer to the research I am doing at the moment – understanding the neuro-immunological mechanisms underlying mental health disorders. While psycho-neuro-immunology has always been my main research interest and focus, over the years, I have had the opportunity to connect with neuroscientists working in the field of nutritional psychiatry, and I immediately felt captivated by how diet/nutrition can regulate our immune response and ultimately affect our mental health.

What impact do you hope to achieve in your field by focusing on specific research topics?
I do hope my research will be able to provide novel insights into the neuroinflammatory mechanisms underlying mental health disorders and, as a consequence, to contribute to the development of novel and more personalized therapeutic approaches for patients with mental health disorders with sub-chronic levels of inflammation, who are not responding to current antidepressant treatments.

Please tell us more about your current scholarly focal points within your chosen field of science.
Currently, my team of researchers and I are focusing on several projects. For our NIHR-funded study, we are gaining mechanistic insights on how long-COVID-19 affects the brain via exposing human brain cells directly to blood from these patients – this is indeed a follow-up study from a previous Rosetrees Trust-funded project where we tested how peripheral inflammation in acute COVID-19 patients with neurocognitive symptoms was affecting brain neurogenesis. In parallel, for our European-funded project, EarlyCause, we have developed multiple in vitro models of early life stress (ELS) using cells from the brain and the body in order to investigate causative mechanisms linking ELS to the development of psycho-cardio-metabolic multi-morbidities. Finally, we are in the last stage of the Symprove study, a project funded by Parkinson's UK, which aims to uncover the neurobiological mechanisms underlying the effect of oral Symprove (a probiotic) for the management of non-motor symptoms, including depression and anxiety, in people with Parkinson's. 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?
Over the years, I have been involved in many new projects and supervision roles. The two habits I have developed most are working hard and planning ahead. There are times when multiple deadlines are approaching, and organizing tasks in advance has allowed me to perform at my best without experiencing anxiety or feeling pressure. Science is fun, and I value celebrating every success, no matter how big or small it is – this is something I learned over the years working with Carmine Pariante. I do the same with the people who are working with me.

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?
Inclusion, for me, is a fundamental aspect of science. I genuinely believe there should be no sign of cultural, social, or ethnic barriers within our scientific community. As a woman and a mother, I also condemn any form of pregnancy or maternity discrimination.

What do you most enjoy in your capacity as an academic or research rising star?
The freedom to develop and investigate your own scientific hypothesis, the excitement of creating new collaborations every day, and the privilege to work with amazing people and scientists.

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 spending time and playing with my daughter; it gives me much joy – I also recently realized that it involves much physical activity, precisely what I need for my mental health. I come from a small town near the sea in Italy, so it is inevitable not to mention that I am constantly searching for a sunny beach, hot weather, and blue sky, so whenever I can, I fly back to Italy to remind myself of those scenarios.

Part 2: Alessandra Borsini – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Being surrounded by my family.

What is your greatest fear?
Not to be surrounded by my family in difficult times.

Which living person do you most admire?
Not a specific person, but anyone who managed to find a balance in life.

What is your greatest extravagance?
My interest in aviation and karaoke.

What are you most proud of?
Being a mum and a researcher.

What is your greatest regret?
I would have loved to visit more remote destinations, but there is still time.

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

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

What do you consider the most overrated virtue?
Perhaps confidence.

What is your favourite occupation (or activity)?
I love walking through the streets of central London.

Where would you most like to live?
In a sunny and hot place, by the sea.

What is your most treasured possession?
My memories of the time spent with my grandmother.

[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.

When and where were you happiest? And why were you so happy then?
Now is the happiest time of my life, as I am a wife, mum, and an active scientist.

What is your current state of mind?
I feel serene.

What is your most marked characteristic?
I am a reliable person, both in personal and professional relationships.

Among your talents courses, which one(s) give(s) you a competitive edge?
I am very persistent and do not give up easily.

What do you consider your greatest achievement?
I have developed and led an entirely new MSc course in Psychology and Neuroscience of Mind-Body Interface, which launches this September 2024. For further information on this exciting new programme, click on this link.

If you could change one thing about yourself, what would it be?
I often ask too much of myself.

What do you most value in your friends?
Honesty.

Who are your favourite writers?
Patrick McGraph, Doris Lessing, Paulo Coelho.

Who are your heroes of fiction?
Sherlock Holmes.

Who are your heroes in real life?
Men and women who are committed to their families and their community

What aphorism or motto best encapsulates your life philosophy?
Per aspera ad astra.

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INNOVATORS & IDEAS: RESEARCH LEADER

Udo Dannlowski: Brain structure and function in the long-term course of mental disorders

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Keywords: Neuroimaging, psychiatry, major depression, disease trajectories

Udo Dannlowski is a psychiatrist, psychologist, and translational neuroimaging researcher whose work intersects clinical psychiatry, genetics, data science, and systems neuroscience. His academic endeavors are driven by a commitment to unraveling the complex biological and genetic mechanisms underlying long-term disease trajectories of affective disorders, including depression and anxiety. Dannlowski's use of brain imaging technologies, such as multimodal MRI, to explore the structural and functional anomalies in patients with these disorders in longitudinal cohorts over several years of follow-up with machine learning techniques has significantly advanced our understanding of brain mechanisms in mental disorders. Dannlowski is recognized for contributing to psychiatry and neuroscience, substantially impacting theoretical understanding and clinical practice. Since 2019, he has been heading the Institute for Translational Psychiatry in Münster, Germany, together with the clinical Section for Transition Psychiatry at the Department for Mental Health. We are privileged to present the Genomic Press interview with Professor Dannlowski, who has offered to share insights from his esteemed career and personal experiences for our readers' benefit.

Part 1: Udo Dannlowski – Life and Career

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

When I was asked as a kid what I wanted to be when I grew up, the answer always included "scientist" to some degree – starting with "cave explorer," "dinosaur scientist," or archeologist. Though I was a first-generation academic, there was never a question of whether I wanted to join a university, and I struggled to choose my subject area. With interests in computer science, psychology, literature, medicine, and biology, I studied both medicine and psychology and started neuropsychological studies in depression as a medical student. Combining research and clinical duties proved to be the most sustaining interest so I became a clinical scientist, now heading a research institute as well as a clinical section.

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?

Before becoming a research group leader, I had close and trustful relationships with my supervisors, who eventually became friends. I saw them struggling with several parallel, partly unrelated, and heavily underfinanced projects – and decided that I wanted to do it differently. Instead of conducting multiple smaller studies, I combined neuroimaging and genetics with an epidemiological scope in one large cohort with long follow-up periods. While this was risky at an early career stage in a dynamic academic setting, it was the birth of the Münster Neuroimaging Cohort, which is still running 15 years later.

Figure 1. Udo Dannlowski, MD, PhD, Institute for Translational Psychiatry, University of Münster, Germany.

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

Neuroimaging is a highly interdisciplinary area that offers a playground for practically all my research interests. Functional magnetic resonance imaging (fMRI) allowed me to see the brain at work, testing psychological constructs and traits. As a psychiatrist, multimodal imaging was promising for providing clinical correlates of disorders as well as biomarkers or predictors for treatment response. As a data scientist, I found high-dimensional neuroimaging data to be an Eldorado for applying a multitude of analytic strategies, including machine learning techniques.

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

Tackling the translational roadblock by addressing the long-term perspective of patients using within-subjects designs in large longitudinal cohorts. Developing strategies to uncover bio-psycho-social data signatures for understanding, predicting, and ultimately preventing relapses in the long-term course of affective disorders.

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Please tell us more about your current scholarly focal points within your chosen field of science.
One focal point investigates the neurobiological determinants of long-term disease trajectories in major depression using machine learning-based predictive modeling. Highly related, a second focal point is the association of genetic and environmental risk factors for mental disorders with brain structure and function.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
Trust, collegiality, appreciation, and sharing of data and resources were the determinants of successful and fruitful collaborations. These are necessary for conducting long-term research programs such as large-scale longitudinal neuroimaging cohorts. These values lead to lasting, trustful relationships inside and outside the lab with mentors, faculty colleagues, and trainees alike.

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 warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?
Science is nourished by diversity—both as a research area and in terms of the people conducting the research. Diversity needs to be represented much more as a research target and by researchers on the faculty level.

What do you most enjoy in your capacity as an academic or research leader?
I most enjoy the opportunity to foster a culture of curiosity, innovation, and continuous learning. Leading a team of bright, motivated individuals towards discovering new knowledge and developing novel solutions to complex problems is incredibly rewarding. The chance to mentor and guide emerging scholars and researchers, watching them grow and succeed, is a privilege. Furthermore, the collaborative aspect of academia—building interdisciplinary partnerships and networks—enriches the research experience, leading to more comprehensive and impactful outcomes. This role not only allows me to contribute to advancing my field but also to play a part in shaping the future of research and education.

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 like to spend time with my family and in nature on a boat, in the woods, or on a hiking trail.

Part 2: Udo Dannlowski – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
My daily hour of reading books with my 14-year-old daughter – and playing Dungeons and Dragons with her.

What is your greatest fear?
The decline of sanity worldwide and the abuse of power by a few persons at the wrong place.

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

What is your greatest extravagance?
Keeping an old, used, cheap car alive for many years, which is basically an ugly, scruffy, and uninspired wreck.

What are you most proud of?
My two daughters.

What is your greatest regret?
Despite not being a "dinosaur scientist"? Probably trusting a person with a dark triad.

What is the quality you most admire in people?
Being able to laugh about oneself.

What do you consider the most overrated virtue?
True virtues can never be overrated.

What is your favorite occupation (or activity)?
Except for spending time with my kids, the short boat rides to a sundowner at the nearby riverside beer garden, and picking mushrooms in fall.

Where would you most like to live?
Germany is an excellent place to live. South Asia during winter, however, offers even more tempting places to stay.

What is your most treasured possession?
A house with a river jetty and kingfishers breeding nearby.

When and where were you happiest? And why were so happy then?
The years of travelling Asia together with the person who was so brave to marry me later.

What is your most marked characteristic?
Probably a somewhat idiosyncratic humor and not taking myself too seriously.

Among your talents, which one(s) give(s) you a competitive edge?
I would not consider myself competitive, and no specific talent stands out. My goal is probably to attract exceptional people and support their development.

What do you consider your greatest achievement?
Having this incredible group of brilliant people around and hopefully being liked by at least a few of them.

If you could change one thing about yourself, what would it be?
My impatience, particularly with non-academic administrative colleagues.

What do you most value in your friends?
Their existence. And their relentless patience with me.

Who are your favorite writers?
This list might exceed the word limit, starting with Franz Kafka, Hermann Hesse, Astrid Lindgren, Janosch, Douglas Coupland, Stanislav Lem, John Steinbeck, Fyodor Dostoevsky, Max Tegmark, Yuval Harari, Michel Houellebecq, Virginia Woolf, Haruki Murakami, Gabriel García Márquez, Albert Camus, Douglas Adams, ...

[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.

Who are your heroes of fiction?
Land-surveyor K., Pippi Longstocking and Ronja the robber's daughter, Siddhartha, HAL9000, Marvin the robot, Harry Haller.

Who are your heroes in real life?
My grandma, the strongest and wisest person ever walking this planet.

What aphorism or motto best encapsulates your life philosophy?
Odi et amo. Quare id faciam, fortasse requiris. Nescio, sed fieri sentio et excrucior. (Catullus 85)

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INNOVATORS & IDEAS: RESEARCH LEADER

Vicki L. Clifton: Stress, sex, and the placenta: its role in fetal and child development

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Keywords: Pregnancy, placenta, fetus, stress, anxiety, depression

Professor Vicki Clifton, PhD, GAICD, Dip Manag, Dip Counselling, FRSM, is a Mater Research Institute-University of Queensland Amplify Fellow specializing in obstetrics research through clinical trials and basic biology. With 327 publications, h-Index: 61, and over 14,000 citations, her research focuses on stress and maternal asthma during pregnancy, examining their effects on maternal health, placental function, fetal growth, and child health. She is notably recognized for her work on sex-specific placental function and stress responses influencing fetal growth and pregnancy outcomes. Professor Clifton has led her institution's asthma and pregnancy research program, establishing multi-disciplinary, end-user-engaged research programs in Australia and overseas. Her innovative research has advanced our understanding of factors affecting asthma during pregnancy, leading to new models of care and improved fetal outcomes. Her work has influenced national and international asthma management guidelines, identified sex-specific mechanisms affecting maternal-fetal health, and expanded the frontiers of existing knowledge on fetal-neonatal physiology. Through preclinical studies and clinical partnerships, she has rapidly translated findings into practice guidelines and consumer information. She currently leads the Queensland Family Cohort study, a state-wide longitudinal study linking parental and child health outcomes to biological mechanisms. A Fellow of the Royal Society of Medicine, she pioneered women's leadership as the first female President of the Endocrine Society of Australia and the first female Editor of *Placenta* (Elsevier). As an NHMRC Research Fellow (2000–2023), she has secured over $25 million in category 1 grants. We are privileged to have Professor Clifton share her personal and professional insights with our readers in this Genomic Press Interview.

Figure 1. Vicki L. Clifton PhD, GAICD, Dip Manag, Dip Counselling, FRSM, Mater Research Institute-University of Queensland, Australia.

Part 1: Professor Vicki Clifton – 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 greatly influenced by my parents, grandparents, and great-uncle, who taught me about agriculture, marine life, geology, paleontology, plants for food and medicine, and a bit of chemistry while working in my mum's hairdressing salon and understanding why hair ended up curly with a perm. Science was all around me, and it seemed natural to focus on a science degree. I attended the University of Newcastle and was fortunate to have lecturers and mentors who recognized my potential and guided me into postgraduate study. At the same time as starting my postgraduate research degrees, I had 3 babies, with one of my sons dying in mid-gestation. This devastating experience led to the question, "What went wrong?" and eventually led to studying the placenta. I joined the Mothers' and Babies Research Centre at the University of Newcastle and started my PhD examining placental circulation and its regulation by stress hormones. Following my PhD, my family and I were keen on an adventure, so I accepted a postdoctoral fellowship with Prof John Challis at the University of Toronto. This was my first introduction to fetal physiology and stimulated my curiosity for understanding the mechanisms that regulate placental function and fetal growth and survival.

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?

After living in Canada for my postdoctoral fellowship for two years (1995–97), I returned to the University of Newcastle, Australia, where I started

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to examine the role of maternal asthma and stress and its effect on the placenta and fetus (1998–2007). I formed some key collaborations and established the first controlled asthma and pregnancy birth cohort. However, during this time, my first husband died, and after several years of grieving, supporting my children, and feeling lost, I remarried and decided I needed a fresh start. I was Deputy Director at the Mother's and Babies Research Centre, and I had no foreseeable opportunity to be promoted further and gain further leadership experience, so I started to look for new positions at other institutions. I met the Director of the Robinson Research Institute in Adelaide, who invited me to the University of Adelaide to see what I thought of the city and discuss new leadership opportunities. My partner and I fell in love with Adelaide and decided to move. I was appointed Director of Clinical Research at the Lyell McEwin Hospital in Northern Adelaide as the hospital transitioned to a tertiary-level teaching hospital (2008-2015). It was a great experience developing a strategy for introducing research to the hospital and then engaging clinicians in research activity.

After seven years in Adelaide, I was invited to Brisbane to give a talk at the Mater Research Institute. Mater has the biggest maternity hospital and neonatal intensive care unit in Australia, and I was very impressed with its potential for continuing my research. I was offered a position as Program Leader of Mothers, Babies, and Women's Health at Mater, and although I was not considering a move, the offer was too good to ignore in terms of what I could achieve, and the challenge was intriguing. This exciting new adventure would allow me to establish a large birth cohort in the state and increase my capacity to collaborate with fantastic researchers across several Universities and Institutions.

I follow my intuition on when to make a change in my career, and as a result, I have enjoyed the experience of moving to new jobs and exploring new places. I am still in Brisbane and love my role at the Mater Research Institute. Many of my latest leadership roles include Board Director and Secretary of Women's Health and Equality Queensland. I wanted to contribute to improving the lives of vulnerable women, and donating my time to a not-for-profit organization has been a more tangible way to make a difference in the lives of women. This role has also opened up many other great opportunities, including being a part of the advisory panel that developed the Queensland Government's Women's and Girls Health Strategy. At this stage in my career, I continue to focus on my research and work on my favorite organ, the placenta!

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

I started working in asthma and pregnancy research due to my own lived experience. I am an asthmatic, and I had severe symptoms during pregnancy which resulted in adverse outcomes for my babies (1989–91). I found that the clinical care for my asthma, specifically during pregnancy, was lacking. A literature search identified that there was very little research in the field. I was fortunate to be co-located with Obstetrics and Respiratory Medicine at the John Hunter Hospital in Newcastle and started to discuss potential projects with Professor Peter Gibson and Professor Warrick Giles. This led to the establishment of the first controlled prospective birth cohort of pregnant women with and without asthma (1999–2007). Since then, the research in this field has expanded exponentially with the establishment of several different birth cohorts, randomized controlled trials, and epidemiological studies that have translated into significant improvements in clinical practice. The work has morphed into examining the effect of stress on the placenta and fetus, which has led to a greater focus on maternal mental health in pregnancy.

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

Based on the evidence from my research, male and female fetuses are physiologically different, which is partly conferred by the placenta's sex-specific function. Presently, we do not consider the sex of the fetus in Obstetrics. I would like to see sex-specific medicine for pregnancy complications, for the care of preterm neonates, and for the care of newborns. Our work also suggests that maternal physiology in pregnancy varies depending on the sex of the fetus, and I hope the evidence we provide could translate into clinical decisions around interventions for pregnant women based on the sex of the fetus.

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

Currently, we are focused on how the placenta may influence maternal stress, anxiety, and depression. We have discovered that the placenta has 13 different isoforms of the glucocorticoid receptor, with one isoform expressed in the presence of maternal stress, anxiety, and depression that activates an inflammatory response in the placenta in the presence of high cortisol concentrations. Most glucocorticoid receptors inhibit inflammation, so this new finding is surprising. This work may explain why high levels of stress and high inflammation can coincide. Increased inflammation in women with anxiety and depression can act directly on numerous parts of the brain to exacerbate symptoms, and we hypothesize the placenta has a role in contributing to the rise in inflammation with pregnancy and, in turn, influencing mum's brain. We are working on the mechanisms right now; maybe this work will impact the management of perinatal mental health somewhere in the future.

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

Say yes as much as you can. Always stay up to date with the literature, invest time weekly in supporting your team and students, stay connected with your wider network, and communicate clearly. Don't be afraid to ask for what you need or take a risk on an idea, and persevere when you fail. Further your education.

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?

Aboriginal and Torres Strait Islander people of Australia deserve equal opportunity in all aspects of society, including science. Greater investment in culturally appropriate school education for Aboriginal and Torres Strait Islander children that leads them to culturally appropriate University education and academic careers is essential for changing the outcomes for this important population. I am especially passionate about improving the lives of Aboriginal and Torres Strait Islander women and seeing them empowered through education.

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

I love the whole job, but there are three aspects of being an academic that I particularly enjoy. First of all, the data! It is a privilege to think about a problem, formulate a hypothesis, and test it. Second, working with different people locally, nationally, and internationally who have different areas of expertise and think differently from me. Third, and most importantly, being able to mentor and supervise students.

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 an amazing husband, a circle of close friends, and a beautiful family, and most of my free time is spent with them. If I had nothing else going on, I would probably snorkel on the Great Barrier Reef every day. I regret not being a marine biologist some days. Maybe I will do another PhD in marine biology when I retire!

Figure 2. Vicki Clifton and her partner snorkeling on the Great Barrier Reef near Cairns. She reflected on her first reef experience: "We were on an organized tour, and it was a silly tourist picture. However, it makes me smile whenever I look at it because it was an amazing day."

Part 2: Professor Vicki Clifton – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
A healthy family is living their best life.

What is your greatest fear?
Climate change.

Which living person do you most admire?
Many people. Senator Linda Burney, Jane Goodall, and Greta Thunberg.

What is your greatest extravagance?
Long holidays.

What are you most proud of?
My family.

What is your greatest regret?
Not speaking up when I knew something was wrong and not following my intuition when I knew it was right.

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

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

What do you consider the most overrated virtue?
Cleanliness: I despise housework and thrive in creative clutter.

What is your favorite occupation (or activity)?
Snorkeling.

Where would you most like to live?
I already live there: by the ocean in Australia.

What is your most treasured possession?
A cedar bedside cabinet carved by my Great Uncle Peter for my Great Aunty Ciss when they were engaged about 110 years ago. Their love and respect for each other was inspirational.

When and where were you happiest? And why were you so happy then?
I did not realize it was my happiest day until I looked back and found it was never like that again. My closest family and friends, whom I love dearly, were all together at my second wedding. It was a great celebration by the ocean, with the sun shining and the conversation, laughter, food, and wine flowing freely. Since then, I have lost many of my family members to illness, accidents, and aging, so that day will never be recaptured.

What is your current state of mind?
Content but motivated.

What is your most marked characteristic?
Loyalty.

Among your talents, which one(s) give(s) you a competitive edge?
Creativity and perseverance.

What do you consider your greatest achievement?
Translating my research into a tangible outcome for women's health.

If you could change one thing about yourself, what would it be?
Doubt in my ability.

What do you most value in your friends?
Loyalty.

Who are your favorite writers?
William Kotzwinkle and Anita Diamant.

Who are your heroes of fiction?
Ayla in Clan of the Cave Bear by Jean Auels.

Who are your heroes in real life?
Captain Paul Watson and Julian Assange.

What aphorism or motto best encapsulates your life philosophy?
Carpe diem.[2]

Vicki L. Clifton[1]
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[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.

[2] Latin phrase meaning "seize the day" – a call to make the most of the present moment rather than waiting for tomorrow.

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INNOVATORS & IDEAS: RESEARCH LEADER

Euripedes C. Miguel: Risk factors for obsessive-compulsive and other mental health disorders and their treatment and public policy implications

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Keywords: OCD, Developmental Psychiatry, Digital Mental Health, Implementation Science

Euripedes Constantino Miguel is a full, tenured Professor and Head of the Department of Psychiatry at the Faculty of Medicine, University of São Paulo (FMUSP), and an Adjunct Associate Professor at Yale University School of Medicine. He graduated from FMUSP and completed his Psychiatry Residency and PhD at the Institute of Psychiatry at the University of São Paulo. After a postdoctoral fellowship at Massachusetts General Hospital, Harvard Medical School, Professor Miguel returned to Brazil in 1994 to pioneer the Obsessive-Compulsive Spectrum Disorders Program. He leads the National Institute for Developmental Psychiatry www.inpd.org.br, focusing on early identification and intervention of mental health disorders. Since 2023, he has led the National Center for Science and Innovation in Mental Health (CISM) www.cism.org.br, enhancing mental health education and research through innovative solutions and public-private partnerships. This Genomic Press Interview features Professor Miguel's candid reflections on his professional achievements and life's journey.

Figure 1. Euripedes C. Miguel, MD, PhD, Faculdade de Medicina, Universidade de São Paulo, Brazil

Part 1: Euripedes C. Miguel – 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 knew I wanted to become a physician from a very early age. My father, a psychiatrist, served as a role model for me. It was common for my father to bring some of his patients, who were sometimes depressive or psychotic, to our ranch. This provided me with a unique opportunity to observe their recovery as they lived with us. I did what I could to help and was struck by how rewarding these experiences were to my father and me. Thus, my decision to become a doctor was strongly associated with this fulfilling feeling of helping patients. Later, I enrolled in the Faculty of Medicine at the University of São Paulo (FMUSP), the top medical school in Brazil. There, I engaged in several academic activities, including serving as President of the student sports club (Associação Atlética Acadêmica Oswaldo Cruz). The experience of representing students to the Dean and leading in finding ways to pursue common goals was very significant for me, fostering a solid attachment to my medical school. After completing my residency in Psychiatry, I was sure I wanted to become a future leader at FMUSP. This ambition meant becoming a full professor, which required pursuing an academic career, including obtaining a PhD, postdoctoral training abroad, and developing my research skills. Teaching became my passion during this time, especially as I recognized that teaching is the best way to learn. In turn, I realized that conducting research was the best way to develop critical thinking, which allowed me to prepare better lectures. In this way, research became a means to achieve my goals. During this process, I also discovered that conducting high-quality research and gaining deep knowledge in a specific area alongside colleagues was very rewarding and greatly enjoyed.

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?

When I finished my PhD, I was the Chief of the Consultation Psychiatric Service at our Institute of Psychiatry. I chose to do my postdoctoral training at Massachusetts General Hospital primarily because it has one of the area's most renowned departments. However, upon my arrival, I realized that their focus was much more on teaching and clinical care than on research, which was the primary purpose of my scholarship. During this period, I had the opportunity to participate in the OCD Clinic led by Michael Jenike. Although OCD was not an area of interest for me at that time, I saw this as the best opportunity available. To begin in an area where I had no prior background, I started a study group with Scott Rauch and Lee Baer (both from the OCD Clinic), Katherine Phillips, and Barbara Coffey, who was at McLean Hospital nearby. With their help, I developed

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a project focused on the clinical phenomenology of OCD and Tourette Syndrome. During the project's development, I learned that the Child Study Center at Yale was the most productive institution in Tourette Syndrome, with James Leckman being one of the leading figures in this field. I visited Yale to present my project to him and his colleagues (David Pauls and Donald Cohen), and they soon became part of my project, providing the methodological refinement I needed. Several papers resulted from this fruitful partnership, and we have continued our collaborations to this day. Back in Brazil, I helped create a competitive OCD Research group that was one of the most productive in the world for many years. In 2009, a position for Full Professor at FMUSP was announced, and I submitted my application, along with several other colleagues. The opportunity was in Child and Adolescent Psychiatry, although I was an adult psychiatrist. Therefore, my strategy was to propose an innovative project focused on identifying individuals at risk for psychiatric disorders and interventions to mitigate or prevent symptom expression. A few months before the open selection process, Brazil's two main research foundations (CNPq and FAPESP) launched a significant grant opportunity. I applied for that grant with my colleagues Luiz Rohde and Jair Mari (with whom I have been collaborating for more than 25 years) and successfully created the National Institute for Developmental Psychiatry for Children and Adolescents www.inpd.org.br, focusing on the early identification and intervention of mental health disorders in individuals at risk. This grant provided the credentials I needed to become a full, tenured Professor of Child and Adolescent Psychiatry at the Department of Psychiatry at FMUSP – where I have been consistently elected Chair (or Vice-Chair) of the department for the past 15 years. Therefore, I believe that the defining moments that made all this possible involved making the most of the situations I encountered by adapting my skill sets to match available opportunities, choosing the right people to work with, and fostering these relationships for life.

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

What piqued my interest were the opportunities that arose during my career that allowed me to deliver care to those in need in a way that made sense within the larger goal of serving my institution as a leader.

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

To provide new evidence-based treatments that will make a difference in the lives of patients with OCD and their families, and to implement a few tested interventions in mental health care delivery that can be transformed into public policies.

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

I continue to invest in the area where I have published the most, which involves Obsessive-Compulsive Disorder (OCD). My work is mainly focused on clinical phenotypes, their underlying neurobiological signatures, and how this knowledge can be transformed into treatments that provide some relief for individuals with OCD and their families. More recently, I have redirected my focus to the early identification and intervention of mental health disorders in individuals at risk for such disorders. In 2023, we created the National Center for Science and Innovation in Mental Health (CISM) (www.cism.org.br). Through this grant, which receives public and private funding, we aim to identify modifiable risk and protective factors in a cohort study involving individuals at risk for mental health disorders. A fascinating part of this project is the development of scalable digital mental health solutions based on these risk factors that we are testing in pragmatic clinical trials to promote improved mental health. Additionally, other interventions are being tested in individuals who have already been diagnosed but do not have access to treatment. Once their effectiveness is demonstrated, these interventions will be implemented in two separate cities in Brazil, providing evidence for the creation of public policies with the potential to transform the lives of people with mental health disorders and their families.

Figure 2. A moment of joy with my entire family in 2024.

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

Leadership is built not through authoritarianism but by addressing the needs of each team member and fulfilling agreed-upon commitments. This approach recognizes that knowledge is universal and should be shared, which, in turn, produces a team that grows together, leading to greater success.

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?

More than a specific cause, what captivates me are values, such as the idea of seeking, in the most honest way possible, a truth that is only provisional but offers new models that help us move beyond current limitations – even if this provisional truth ultimately proves to be an illusion.

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

I find being able to bring people together around common goals, develop the best in each of them, and act according to previously made agreements keeps people working together for long periods. In short, to inspire an atmosphere of trust.

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?

My mother, Maria Lydia, is 93 years old. My father passed away 15 years ago. I have four children, who are now adults. Three of them are married (Helena, Alice, and André), to my two sons-in-law (Arthur and Luli) and my daughter-in-law (Luciana), respectively. Gustavo, my youngest son, is 17 years old. I have four grandchildren (Tomás, Noah, Dudu, and Laila), with one more grandson expected by the end of 2024. There is nothing I enjoy more than spending time with all of them, if possible, along with my wife, Maria Lúcia. I also enjoy spending time with my close friends. Individually, my main hobby is equestrianism, and I love participating in horse jumping competitions.

Part 2: Euripedes C. Miguel – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
I do not believe in perfect happiness. For me, happiness consists of instants. These instants of happiness occur more frequently when I am close to and interacting with significant people in my life.

What is your greatest fear?
Making wrong choices and losing significant time in my life, especially now that I do not have much left.

Which living person do you most admire?
There are so many: I cannot choose just one.

What is your greatest extravagance?
Practicing equestrianism.

What are you most proud of?
The family and friends I have built over my life.

What is your greatest regret?
I have several. I cannot name the greatest, but I hope I have learned from each one.

What is the quality you most admire in people?
Transparency and generosity.

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

What do you consider the most overrated virtue?
Gratitude.

What is your favorite occupation (or activity)?
Being a doctor caring for patients.

Where would you most like to live?
In my current home.

What is your most treasured possession?
My family.

When and where were you happiest? And why were you so happy then?
I am happiest when I am gathered around a big table with my wife, my children, their significant others, and my grandchildren – just hanging around. These moments of togetherness and the joy of being surrounded by my loved ones bring me immense fulfillment.

What is your current state of mind?
Unsettled, in a constant search for wisdom.

What is your most marked characteristic?
Energetic, determined, and resilient.

Among your talents, which one(s) give(s) you a competitive edge?
I am good at bringing people together to work towards common goals over extended periods, ensuring that agreements and commitments are fulfilled.

What do you consider your greatest achievement?
That I have a family that choses to be with me when they do not have to be.

If you could change one thing about yourself, what would it be?
I want to be more present and available, particularly to significant people in my life.

What do you most value in your friends?
Genuine warmth and acceptance, allowing me to truly be myself.

Who are your favorite writers?
I do not have a favorite writer. This may be because I do not consider myself an intellectual. Everything I read is associated with practical application, including my research work. Thus, I read extensively on topics related to my profession. I enjoyed novels and suspense books in the past, but now I seek out books that offer wisdom, often recommended by people I admire.

Who are your heroes of fiction?
I have a profound admiration for heroes, both real and fictional. When I was younger, I often imagined myself as a hero. As I got older, the prospect of a heroic death or gaining prestige at the expense of doing something detrimental to myself became less appealing to me. So, I transformed this admiration into a desire to take on leadership roles guided by the principle of leading to serve. This idea was likely instilled in me by the Jesuits during my time at Colégio São Luiz.

Who are your heroes in real life?
My numerous mentors. Among them, I highlight my father, whose example inspired me to become a psychiatrist; during my medical studies, Paulo Vaz de Arruda, who exemplified a loving attitude in the relationship between a professor and a student and whose influence had a transgenerational effect on me; Valentim Gentil Filho, my role model as a physician, demonstrating methodological rigor in research and care for public responsibilities in leadership roles; and James Leckman, who is an example of generosity in sharing knowledge and pursuing projects with social relevance.

What aphorism or motto best encapsulates your life philosophy?
The poem 'Dreams' by Langston Hughes best encapsulates my life philosophy:

> Hold fast to dreams
> For if dreams die
> Life is a broken-winged bird
> That cannot fly.
>
> Hold fast to dreams
> For when dreams go
> Life is a barren field
> Frozen with snow.

Hughes, a leading voice of the Harlem Renaissance, captured profound truths in accessible language. This poem reminds us that our aspirations give life meaning and propel us forward. Throughout my career, I have often returned to these lines when facing challenges, finding in them the strength to persevere.

[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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INNOVATORS & IDEAS: RESEARCH LEADER

Annamaria Cattaneo: Three main questions: Stress, mental, and physical health: Is the gut microbiome the key? Which are the biological mechanisms driving perinatal depression, and how do they affect the mental and physical health of the offspring? Pharmacological and non-pharmacological interventions in reducing the risk of developing mood disorders or in improving symptomatology: Is inflammation the key driver?

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Keywords: Stress, inflammation, gut microbiome, interventions, biomarkers, mood disorders

Annamaria Cattaneo is an Associate Professor at the University of Milan, Department of Pharmacological and Biomolecular Sciences, and the Head of the Laboratory of Biological Psychiatry at the IRCCS Fatebenefratelli Institute in Brescia, where she is also Deputy Scientific Director. She is currently associate editor of *Brain, Behavior, & Immunity—Health*, an official journal of the Psychoneuroimmunology Research Society. She dedicates her research to understanding the complex interplay between early life adversities and the development of mental health disorders. Her work focuses on the biological mechanisms, such as neuroplasticity, inflammation, gut microbiome, and epigenetics, that connect early life experiences to mental health vulnerabilities later in life. Recently, Dr Cattaneo has expanded her research to explore the liver-brain axis and its role in the development of comorbidities between mental and physical disorders. Additionally, she is actively involved in identifying peripheral biomarkers associated with the risk of developing mood disorders and treatment response. A significant focus of her current work is on perinatal depression, aiming to uncover the biological, social, and environmental factors that shape the risk for depression during pregnancy and its impact on offspring outcomes. As the Coordinator of the HappyMums Project, a Horizon Europe initiative, she leads efforts to improve our understanding of the biological mechanisms underlying the development of depressive symptoms in pregnancy and the efficacy of interventions. Dr Cattaneo's passion for her work extends beyond the laboratory, as she actively engages in dissemination activities to raise awareness about mental health issues among the general population. Through events like the *HappyRun* in the Monza Park and *Luci e Ombre* / *Lights and Shadows*, she brings together science, art, and community to promote mental well-being. In this "Genomic Press Interview," Annamaria Cattaneo kindly shares insights into her life and impressive career, providing our readers with a glimpse into the driving force behind her ground-breaking research and tireless efforts to advance our understanding of mental health.

Figure 1. Annamaria Cattaneo, PhD, University of Milan and IRCCS Centro San Giovanni di Dio – Fatebenefratelli, Italy.

Part 1: Annamaria Cattaneo – Life and Career

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

From a young age, I have been deeply drawn to scientific inquiry. This passion has shaped my academic journey, guiding me toward disciplines like molecular biology and pharmacology.

Growing up, I was always curious about how things worked. However, it was only in high school that I truly realized the depth of my interest. I had a biology teacher who brought the subject to life, explaining complex concepts in a way that made them fascinating and accessible. I started to develop an interest in the field of medicine. However, in the way, I wanted to know more about the causes of underlying pathologies and ways to treat them successfully. In that period, I also lost a family member because of an illness (cancer), and this event strengthened my determination to explore and discover the origins of certain medical conditions and to seek ways to prevent or treat them. I understood the power of science to not only answer questions but also to ask new ones. This realization drove me to pursue a career in research, where I can explore the unknown and

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contribute to expanding our understanding of the world. These experiences, combined with a deep-seated curiosity and a drive to make a meaningful impact, have fuelled my passion for science ever since. They set me on a path that has been both challenging and incredibly fulfilling, and they continue to inspire me in my work today.

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?

Although I initially focused on cancer research during my studies at the University, my career path shifted after a one-year research traineeship in a laboratory specializing in preclinical mental disorders studies. This experience sparked a new direction in my research interests. Also, immediately after my degree in pharmacy, I had the opportunity to pursue a PhD in molecular genetics and apply it to medical sciences at a psychiatric institute, enabling me to continue focusing on mental disorders. Conducting my PhD research at a psychiatric hospital profoundly impacted my career trajectory, as it deepened my understanding of the critical role that science and research play in advancing the mental health field. This experience not only intensified my passion for the field but also allowed me to develop critical aspects of my research independently. During my PhD, I honed essential skills such as grant writing and student supervision, which have been instrumental in my career. Another important moment was in 2013, when I secured my first grant—an ERANET Neuron grant—which not only funded my own salary but also supported the first two researchers who joined my team. This marked the birth and growth of my lab, which now includes 21 researchers, ranging from undergraduate students to PhD candidates and postdoctoral fellows, and more than 15 grant-funded projects.

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

During my career, I have always been interested in the link between adverse experiences in early life—such as childhood and adolescence—and the onset of mental illnesses in adulthood. The birth of my three children has significantly enriched my life and sharpened my scientific focus on the profound biological changes in women during sensitive periods such as pregnancy and post-partum. Different lines of research highlight the crucial impact of the perinatal period on long-term developmental outcomes in children. This has deepened my scientific interest in understanding how stress and other adverse exposures during the perinatal period might influence the immediate health of mothers and their children and the potential transgenerational effects. Furthermore, given the significant role of the environment in shaping both individual vulnerability and resilience, I am particularly interested in investigating postnatal factors that may serve as moderators and protectors against risks established in utero that can arise from maternal mental illness or high-stress exposure during pregnancy. These postnatal protective factors could be essential in potentiating resilience, and indeed, my research focuses on how these postnatal influences can potentially mitigate or buffer the adverse effects of prenatal stressors, ultimately promoting healthier developmental outcomes.

My research now seeks to elucidate the complex biological mechanisms that mediate these impacts, including hormonal, inflammatory, and epigenetic changes, to inform more effective interventions and preventive strategies.

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

The several projects I'm focusing on all share a common goal: to improve the well-being of individuals with mental disorders or those who are at high risk of developing these pathologies. Much of my research focuses on identifying biomarkers in blood or saliva, which can be pivotal in enhancing clinical practices for prevention, diagnosis, and treatment. Recently, I've expanded my work to incorporate AI tools, aiming for more direct and non-invasive impacts on public health. For instance, the projects focused on perinatal psychiatry include an app designed to remotely gather different data from mothers, monitor and enhance lifestyle choices to promote mental well-being during pregnancy, and continuously assess the effectiveness of treatments.

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

My main scientific interest lies in exploring the roles of inflammation, stress, and, more recently, the gut microbiome. A better understanding of the alterations in these biological processes that can be observed in patients suffering from both mental and physical illnesses is pivotal for the development of personalized interventions. For instance, it's common to find that patients with depression have undergone stressful events, exhibit heightened central and peripheral inflammation, and experience intestinal dysbiosis. Additionally, some of these patients do not respond to conventional drug treatments. This evidence drives my curiosity to understand how these fundamental mechanisms are interconnected and how they influence responses to pharmacological interventions. My goal, as I have mentioned, is patient care: by delving deeper into these mechanisms, I hope to contribute to optimizing therapeutic approaches, potentially reducing the need for patients to endure multiple, often unsuccessful, treatment trials.

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

During my studies and postdoctoral experiences, I learned the importance of maintaining rigorous scientific methods, ensuring that all experiments are meticulously designed and executed precisely and accurately. Now, as a lab leader, I prioritize upholding these standards, not only for myself but also for the researchers I mentor. This discipline is fundamental to publishing reliable papers and ensuring that our results can be reproducible by others, above ourselves, which is crucial for advancing scientific knowledge.

I am also dedicated to conducting all work with transparency and honesty, ensuring that every result is reported accurately. Upholding these ethical standards is essential for maintaining the credibility of our research.

Additionally, I have also learned the importance of curiosity, collaboration, and perseverance, values that I try to disseminate to people in my lab. By regularly engaging with high-quality research publications, we can feed our intellectual curiosity and expand our knowledge, allowing us to develop new ideas and approaches. Research cannot be done by a single researcher/individual: interacting with others is essential to refining our work and making our projects more competitive. The exchange of ideas often leads to breakthroughs that would only be possible. Perseverance is equally crucial. Consistent, hard work—approached with determination rather than superficiality—is the key to producing high-quality research that leads to impactful publications. I also learned the importance of mentorship. Therefore, I actively work to support the growth of younger researchers like my mentors supported me. I prioritize fostering a learning environment where everyone feels empowered to succeed.

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?

I feel perfectly aligned with the priorities adopted by Genomic Press.

What do you most enjoy in your capacity as a research leader?

I am incredibly fortunate to be a scientist. What I most enjoy as an academic and researcher is the opportunity to explore uncharted scientific territories and contribute knowledge that can have a tangible impact on patients' lives. I take great satisfaction in developing projects and

designing interventions to improve patients' well-being and quality of life, above their symptoms, and in inspiring the next generation of researchers.

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 spending time with my family and traveling. Our home setting encourages outdoor activities in nature, such as walking or having picnics in the nearby mountains. I plan trips to enjoy quality time together, ideally by the seaside whenever possible. I also organize special outings with just one of my children, allowing me to focus on each of them individually. For example, when I travel for conferences abroad, I sometimes bring my daughter to have some one-on-one time together. Last year, I also took my second child, who was eight years old, with me to Turin because I had a talk there. During my free time, we visited the Juventus stadium, hoping I could persuade him to switch allegiance to my favourite team. Unfortunately, my efforts failed—he remains a steadfast Inter fan. We even stopped by the Juventus shop to buy a jersey, but when the staff asked which name to put on it, he boldly requested the name of an Inter player. I truly wanted to disappear right there—on the spot.

Part 2: Annamaria Cattaneo – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
My idea of happiness is connected to small, simple moments—those brief, individual experiences or events during the day, such as a text message, a hug, a smile, coming back home after a tough working day, or even an email saying that a submitted paper has been accepted for publication or a symposium accepted for a conference. To me, happiness also means peacefulness and the absence of worries.

What is your greatest fear?
As trivial as it may sound, my greatest fear is death. Death feels insurmountable, unlike other challenges we may face, which can often be overcome, tolerated, or resolved.

Which living person do you most admire?
It's a person very close to me who, despite he had to face difficult experiences, he always finds a way to smile and to stay positive. When negative things happen to me, he always encourages me and oblige me to focus on positive aspects I have.

What is your greatest extravagance?
Balancing a career as a scientist with raising three young children.

What are you most proud of?
The passion and enthusiasm I put into everything I do: I am a mom of three young kids and a scientist managing a lab with more than 20 researchers.

Figure 2. Dr. Annamaria Cattaneo enjoying a sunny day by the sea, her preferred living environment. The image captures Dr. Cattaneo smiling warmly while wearing a woven sun hat, embodying the calming and inspirational atmosphere she describes as her ideal setting. The clear blue sky and glimpse of colourful foliage in the background hint at the seaside location she finds so appealing for its soothing waves, refreshing breezes, and invigorating sunlight.

What is your greatest regret?
I have yet to be able to renovate my parents' house, which is where I would love to move with my family.

What is the quality you most admire in people?
Respect, honesty, and transparency.

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

What do you consider the most overrated virtue?
Modesty.

What is your favourite occupation (or activity)?
Scientific dissemination is certainly one of my favourite activities in the working environment, whether it is done in the most classic way or through more original, pleasurable, and entertainment activities. The idea is, therefore, to reach not only the scientific community but also young people and people in general.

Where would you most like to live?
A city by the sea is my preference. The sound of the waves, the sea breeze, and the sunlight create a calming atmosphere and serve as a source of inspiration (Figure 2).

What is your most treasured possession?
It's a travel souvenir, specifically a bag woven from palm leaves I brought back from my trip to Tanzania.

When and where were you happiest? And why were so happy then?
The birth of my children is one of the most joyful moments of my life, because this filled me with love and gratitude. It has forever changed the way I view the world and people around me.

[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 current state of mind?
Mostly positive.

What is your most marked characteristic?
My most distinctive trait is perseverance and the ability to bounce back.

Among your talents, which one(s) give(s) you a competitive edge?
A talent that sets me apart is my emotional intelligence. My ability to understand and regulate both my own emotions and those of others enables me to navigate complex interpersonal dynamics, foster strong relationships, and lead teams effectively, even in difficult circumstances.

What do you consider your greatest achievement?
A significant achievement in my career has been my progress over the years. In 2013, I secured my first grant—an ERANET Neuron grant—which funded my salary and supported the first two researchers who joined my team. Today, my lab has grown to include 21 researchers, including PhD students. This growth is a testament to years of perseverance, dedication, and hard work, as well as the support my family received. I could never be a scientist in my career and, at the same time, raise three kids without the support from my family.

If you could change one thing about yourself, what would it be?
If I could change one thing about myself, it would be to strike a better balance between directness and diplomacy. While I value honesty and transparency, I recognize that sometimes a more nuanced approach is needed to communicate effectively and maintain harmonious relationships.

What do you most value in your friends?
In my friends, I appreciate trust, honesty, and empathy.

Who are your favourite writers?
Honestly, I have not had much time to read books lately. A few years ago, when I had more free time, I read several books by Bambaren and King Albon.

Who are your heroes of fiction?
My favourite hero is Catwoman, a complex and intriguing character known for agility, cunning, strength, and independence. As a master thief with a robust moral code, she often straddles the line between hero and anti-hero. Her feline elegance and originality make her a formidable presence, while her depth and duality reveal a layered personality that challenges conventional notions of good and evil.

Who are your heroes in real life?
Jane Goodall: A renowned primatologist and conservationist, Jane Goodall's pioneering studies on chimpanzees revolutionized our understanding of animal behaviour. Her lifelong dedication to wildlife conservation and humanitarian work has made her a leading environmental and animal rights advocate.

What aphorism or motto best encapsulates your life philosophy?
Here I would like to cite a song from one of my favourite Italian singers, Vasco Rossi which says: *"I want a reckless life; I want a life like in the movies; I want a life where it's never too late; One of those where you never sleep; I want a life; You'll see what a life it will be, uh."*

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INNOVATORS & IDEAS: RESEARCH LEADER

Celso Arango: The future of psychiatry inevitably depends on primary prevention

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Keywords: Prevention, child and adolescent psychiatry, risk factors, resilience, neurodevelopmental disorders

Dr. Celso Arango stands as a preeminent authority in psychiatry, wielding considerable influence through his multifaceted roles. As Director of the Institute of Psychiatry and Mental Health at Hospital General Universitario Gregorio Marañón and Professor of Psychiatry at the Universidad Complutense de Madrid, he spearheads Spain's advancements in mental health research and treatment. Dr. Arango's expertise resonates globally, reflected in his visiting professorships at renowned institutions, including the University of California, San Francisco, the University of Maryland, and King's College London. His commitment to international collaboration, evidenced by partnerships with over 100 institutions worldwide, significantly propels the global psychiatric community forward. Dr. Arango's exceptional contributions have garnered prestigious accolades, notably his election as the youngest member of the Royal National Academy of Medicine in Spain and his recent induction into the National Academy of Medicine in the United States. At the core of his research efforts lies a dedicated focus on early-onset psychosis and neurodevelopmental disorders in young individuals, work that not only advances scientific understanding but also offers tangible hope for improved treatment outcomes. Dr. Arango's unique blend of clinical expertise, research acumen, and academic leadership positions him at the vanguard of innovation in mental health care, potentially revolutionizing our approach to understanding and treating psychiatric disorders across the lifespan. In this exclusive Genomic Press Interview, Dr. Arango shares insights on his life and career, offering our readers a glimpse into the mind of one of psychiatry's most influential figures.

Part 1: Celso Arango – Life and Career

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

When I was a child, I remember helping my father, who was a psychiatrist, by placing the required stamps on his prescriptions. I also listened to his fascinating and curious stories about clinical cases he attended worldwide. I have always been obsessed with the truth and have never liked people who expect their opinions to be accepted without data to back them up.

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?

I have always been restless and driven by the search for new challenges and opportunities. Although I was born in Palma de Mallorca, I studied medicine in Oviedo, in northern Spain, where my father's family is originally from, as well as in Manchester, in the United Kingdom. After completing my residency in psychiatry, I pursued a fellowship in schizophrenia research at the University of Maryland. There, I met my mentor, Professor William Carpenter, who has guided me ever since.

Figure 1. Celso Arango, MD, PhD, Hospital Gregorio Marañón, UCM, CIBERSAM, Madrid. Spain.

Upon my return to Spain, I began my work with the firm belief that strength lies in unity, modesty, and collaboration. I became the first scientific director of the Spanish Networked Center for Mental Health Research (CIBERSAM), and, together with other outstanding psychiatrists in Spain, such as Eduard Vieta, I helped ensure that Spanish psychiatry collaborated across a network with many other scientific disciplines. I currently run what is likely the largest department of psychiatry in the country, with over 350 staff members.

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

My research has evolved, likely reflecting my belief that research should be dynamic and informed by its results. I initially focused on schizophrenia

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Figure 2. Celso Arango participating in the Lanzarote International Half Marathon on the Island of Lanzarote, Canary Islands, Spain. Amidst the iconic palm trees of the island, Dr. Arango is captured in full stride, flashing a bright smile and a thumbs-up to onlookers. His enthusiastic engagement in this challenging event reflects the energy and determination he brings to his pioneering work in psychiatry. The vibrant island setting provides a striking contrast to Dr. Arango's usual clinical environment, highlighting his ability to balance rigorous professional pursuits with an active lifestyle.

and first psychotic episodes, primarily in child and adolescent populations. I then became interested in secondary prevention of psychosis, followed by research into prodromal stages and risk factors for psychosis. Currently, I am focused on primary prevention of mental disorders, exploring universal, selective, and indicated primary prevention strategies.

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

I have come to understand that there are no specific risk or resilience factors for particular disorders and that the increase in the incidence and prevalence of mental disorders can only be addressed, as in many other areas of medicine, through primary prevention.

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

We need to learn to work with basic researchers to understand the mechanisms through which risk factors shape brain function and gene expression, and with many other specialties and disciplines to effectively prevent mental disorders by minimizing risk factors and enhancing resilience. We must collaborate with obstetricians, neonatologists, pediatricians, educators, employers, policymakers, sociologists, and others.

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

I greatly appreciate flexibility, originality, and disruptive thinking that questions widely accepted beliefs. Values such as honesty, humility, and punctuality are always top priorities for me. I love being surrounded by people who know more than I do and having the opportunity to learn something new daily.

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?

Unfortunately, the Spanish system has traditionally been influenced by nepotism and established connections rather than meritocracy. It is an unjust system that prioritizes one's last name and personal connections over individual merit. This system has harmed generations of young talent who have had to emigrate or give up on their dreams.

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

I greatly enjoy teaching psychiatry to fifth-year medical students and watching as young researchers I have trained now lead their investigations.

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 playing sports, especially running, as it helps me relieve much stress. I also love participating in my children's activities, such as soccer and paddle tennis. We try to take a family trip every year, and I enjoy our summer break in Viveiro, a village in northern Galicia where we have a family home. Time seems to pass much more slowly there.

Part 2: Celso Arango – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?

I do not believe in perfect happiness; its pursuit can only lead to frustration and dissatisfaction.

What is your greatest fear?

I worry that my child's needs, as someone with severe intellectual disabilities, will not be met when I am no longer in this world.

On a broader level, my greatest fear is how populism, post-truth thinking, and extreme, reductionist positions, which even affect psychiatry, have been gaining ground in recent times.

[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.

Which living person do you most admire?
On a professional level, my mentor, William Carpenter, has been instrumental, while on a personal level, my wife and children have been my greatest support. Additionally, figures like Ramón y Cajal and Gregorio Marañón inspire me beyond the personal realm.

What is your greatest extravagance?
I am not sure if it is considered an extravagance these days, but I am a big fan of my football team, Atlético de Madrid, and I feel quite upset when they do not play well.

What are you most proud of?
I feel very proud of the recognition I receive from grateful patients for what I have been able to do for them.

What is your greatest regret?
Not having been closer to my father in his last years.

What is the quality you most admire in people?
Intelligence, compassion, and sincerity.

What is the trait you most dislike in people?
Lack of integrity.

What do you consider the most overrated virtue?
The ones that should never be considered virtues: power and money.

What is your favorite occupation (or activity)?
I greatly enjoy my clinical work and the feeling that I am helping my patients and their families. I also truly enjoy promoting philanthropy for child psychiatry, which has given me the opportunity to meet wonderful people like Alicia Koplowitz. I also love singing with my musician friends!

Where would you most like to live?
In Spain. I will always live in Spain even though I may work abroad temporarily.

What is your most treasured possession?
The love of my family and the friendship of my friends.

When and where were you happiest? And why were so happy then?
I was very happy during my university studies, in a time that felt freer from responsibilities and worries, surrounded by people with whom I formed deep friendships that persist to this day.

What is your current state of mind?
More at peace than ever, with new challenges that excite me, and focusing more on what I genuinely believe is worthwhile.

What is your most marked characteristic?
I am quite reliable and try to be fair to those around me.

Among your talents, which one(s) give(s) you a competitive edge?
To grow in the face of adversity and never give up on anything. To be a dreamer who fights fiercely for their dreams.

What do you consider your greatest achievement?
To fight against nepotism in my country and strive to ensure that many different people collaborate toward common goals. Additionally, the creation of the specialty of child and adolescent psychiatry in Spain after meeting with nine consecutive health ministers!

If you could change one thing about yourself, what would it be?
Probably spending more time with my children when they were young.

What do you most value in your friends?
That they show up when I need them the most.

Who are your favorite writers?
Gabriel García Márquez, Maggie O'Farrell and Philip Roth.

Who are your heroes of fiction?
More than heroes, one of the things I enjoy the most is watching the films of the Marx Brothers.

Who are your heroes in real life?
Volunteers who invest their time in helping those in need, and individuals who leave behind all material possessions to assist those they do not know.

What aphorism or motto best encapsulates your life philosophy?
Surround yourself with people who are better than you.

Celso Arango[1]
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INNOVATORS & IDEAS: ACADEMIC LEADER

Nancy Jane Rothwell: Brain inflammation and the path to leadership

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Keywords: Obesity, brain inflammation, stroke, leadership, science careers, academic innovation

Breaking barriers in both the lab and the boardroom, Dame Nancy Rothwell has shaped modern British science in ways few others have. Beginning her research journey at the University of London, she made a pivotal move to the University of Manchester in 1987 – a decision that would forge an extraordinary partnership spanning over three decades. During her early career, she followed her scientific curiosity into the intricate world of fat cells with groundbreaking research that cracked open our understanding of how the body regulates its weight through thermogenesis and brown fat metabolism, providing crucial insights into obesity and cachexia. Then, in a bold pivot that would define the next phase of her career at Manchester, she turned her attention to the brain's inflammatory response in stroke and other neurological conditions, conducting pioneering research that bridged the gap between basic biology and clinical applications. Her scientific brilliance earned her Fellowship in the Royal Society, marking her place among Britain's most elite scientists. Her deep connection with Manchester deepened further when, without planning it, she found herself making history in 2010 as the University's first female President and Vice-Chancellor, steering one of Britain's largest universities through fourteen years of growth and transformation until 2024. Her leadership style, marked by the same curiosity and determination that drove her research, helped position Manchester as a global powerhouse in higher education. Now, as the University's Campaign and External Relations Ambassador, she sits down with Genomic Press to share what she has learned about science, leadership and why sometimes the best discoveries come from taking the road less travelled – offering readers a rare glimpse into the mind of someone who has excelled at both groundbreaking research and institutional leadership while helping build Manchester into a world-leading centre of academic excellence.

Part 1: Nancy Rothwell – 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 interest in science was first sparked at the age of about 6 by my father, a biology teacher who kept lots of specimens in jars at our house. When I was 9, I missed about 18 months of school due to illness. Then, I started to read some of his science books and began to draw.

In fact, I dropped biology when I was 14 because I found the plant science part boring (sorry, botanists) and instead took Maths, Physics, Chemistry, and Art for A levels. My first career choice was art, but my kind teacher said I wasn't good enough to make a decent living as an artist. My second choice was Maths, but I decided this could be unsociable (sorry, mathematicians). Ultimately, I studied Physiology at Queen Elizabeth College (now part of Kings), University of London.

Figure 1. Nancy Jane Rothwell, BSc, PhD, DSc, University of Manchester, UK.

I had no career plans at all until I undertook a final-year research project on fat metabolism. I was quickly hooked on research, and I undertook a PhD in thermogenesis and body weight regulation. This was followed by a long career in research in London and, from 1987, in Manchester.

A pivotal moment was securing funding from the Royal Society for a 10-year University Research fellowship, which gave me the freedom to pursue any research, move institutions a few years later to Manchester, and change fields.

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 never had any plans to take on any leadership roles, though along the way of my research, I did happen to take on some roles such as head of the division of Neuroscience in Manchester, then Vice-Dean for Research for the School of Biological Sciences and several external roles on national bodies such as the MRC, Royal Society, Cancer Research UK and for nine years as a non-executive director of AstraZeneca.

All that changed in 2004 when the Victoria University of Manchester and UMIST merged and a new President and Vice-Chancellor, Alan Gilbert, arrived from Melbourne and asked me to be Vice-President for Research for the University. I was reluctant since I then held an MRC Research Chair and had an extensive and thriving research group. I was persuaded and thoroughly enjoyed it. In 2008 I (again reluctantly) became Deputy President and Vice-Chancellor of the University. Over the next two years, Alan's health declined, and I had to step in increasingly. In 2010 I was again

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persuaded to apply for the role of President and Vice-Chancellor, which I served as for 14 years until 2024.

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

The first part of my research career was in thermogenesis and metabolism, an interest piqued by a research project as an undergraduate with Professor Mike Stock, who later supervised my career.

A further pivotal moment occurred after I moved to Manchester, where I investigated the impact of infection, injury, and disease on metabolism and body temperature. We used a rodent stroke model to test the hypothesis that the cytokine interleukin-I (IL-1) caused hypermetabolism and fever, which are common after brain damage. Our hypothesis proved correct, but we had to do one last 'control experiment' to check that the IL-1 antagonist (IL-1Ra) did not affect the extent of damage caused by stroke. To our surprise, the damage was greatly reduced by IL-1Ra. From that moment on, I chose to leave the field of metabolism and research neuroimmunology and brain inflammation.

What were the key impact areas of your research topics?

In the first part of my career, I demonstrated that overfeeding rodents led to an increase in diet-induced thermogenesis and activation of brown fat, which is very similar to the effect of the cold. Hence, some animals remained lean despite an increase in energy intake, while other similar strains became obese.

Later, the main impacts showed that an inflammatory molecule contributed to brain damage, which was not known then. As a result, we understood some of the mechanisms of that damage and its clinical implications.

Could you tell us more about your most relevant focal points within your chosen field of science?

A focal point in understanding energy balance and body weight regulation is the recognition that involuntary energy expenditure and energy intake contribute to overall energy balance.

In neuroimmunology, there was a growing recognition of the importance of the immune system and inflammation in brain diseases.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences, that you have maintained throughout your life?

Honesty, integrity and openness. Just occasionally being open means that you will be 'scooped,' but on many more occasions, it will help in valuable steps forward, insights, and new collaborators and friends.

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?

The scientific community still lacks diversity. Gender balance has improved since I was training, at least in biology, but the diversity of ethnicity, background, and geography is still poor.

What have you most enjoyed in your capacity as academic or research leader?

Undoubtedly, training young scientists and clinician scientists. I have supervised over 50 PhD students, several of whom are now research leaders and professors. Every few years, we meet up for a fantastic reunion.

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?

Spending time at our house in Sweden surrounded by forests and lakes. I have also developed a passion for gardening in the last few years.

Figure 2. A striking new landmark on Manchester's campus, the Nancy Rothwell Building cuts an imposing figure against the city's skyline. What began as an ambitious engineering hub has become a fitting tribute to one of the University's most influential leaders. Named in 2024 to honor Dame Nancy's remarkable 14-year tenure as Vice-Chancellor, this seven-story powerhouse is now home to thousands of budding engineers and scientists. The building's sleek black exterior, captured in the top image, contrasts with the intimate glimpse below of its dedication plaque and time capsule – a thoughtful touch that links the building's cutting-edge facilities with the rich history of innovation at Manchester.

Part 2: Nancy Rothwell – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?

Being with friends and family and having a rewarding job where you feel you can make a difference.

[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 greatest fear?
I do not really have a greatest fear, but perhaps having a highly debilitating disease such as the great scientist Professor Sir Colin Blakemore suffered.

Which living person do you most admire?
Sir David Attenborough was an amazing science communicator but also a lovely and humble person. He came to visit me during rehearsals for the Royal Institution lectures that I delivered for the BBC. He brought me his book and confided that the RI lectures were the hardest thing he had ever done.

What is your greatest extravagance?
Fast cars.

What are you most proud of?
Training so many great scientists.

What is your greatest regret?
Being too risk averse during the earlier part of my career. As my colleague Professor Sir Andre Geim (Nobel laureate in Physics 2010) said 'If you follow the trodden path, you may find that all the grass has been eaten'.

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

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

What do you consider the most overrated virtue?
Intellect. Too little scientific emphasis is placed on insight, imagination, and intuitive leaps.

What is your favourite occupation (or activity)?
Discovering new knowledge.

Where would you most like to live?
Where I live now-UK and Sweden, split between city and countryside.

What is your most treasured possession?
I struggled with this one, but maybe it was my mother's wedding ring, which has been passed down through generations.

When and where were you happiest? And why were so happy then?
When I was in a lab coat early in my career because I was discovering things for myself rather than just supervising them, and when I was on a boat in a lake in Sweden because it was so quiet and peaceful.

What is your current state of mind?
Calm but usually busy.

What is your most marked characteristic?
My mother said being organized, but my partner (of over 50 years) would say optimism.

Among your talents, which one(s) give(s) you a competitive edge?
Perseverance and optimism.

What do you consider your greatest achievement?
Being elected a Fellow of the Royal Society.

If you could change one thing about yourself, what would it be?
Be more focused, but I like variety.

What do you most value in your friends?
Loyalty.
Who are your favourite writers?
Sir Peter Medawar, Arthur Conan Doyle, and, a long time ago, Enid Blyton.

Who are your heroes of fiction?
I could not answer this one because it changes depending on what I read.

Who are your heroes in real life?
Sir David Attenborough, Dame Bridget Ogilvie, Sir Peter Medawar.

What aphorism or motto best encapsulates your life philosophy?
Do as you would be done by.

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PERSPECTIVE

Sterol biosynthesis disruption by common prescription medications: critical implications for neural development and brain health

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Sterol biosynthesis is essential for cellular function, producing not only cholesterol but also critical bioactive molecules that regulate cell signaling, growth, and membrane function. In the brain, cholesterol metabolism operates independently behind the blood–brain barrier, maintaining its own homeostatic balance. An emerging concern in clinical pharmacology is the discovery that many common prescription drugs unintentionally interfere with post-lanosterol sterol synthesis pathways. While acute effects of these medications are documented, their long-term consequences for brain development and function remain unclear. Studies using cell cultures and mouse models indicate heightened risk during pregnancy, where drug-induced sterol disruption may interact with genetic factors from both mother and fetus, particularly when multiple medications are prescribed. This significant research gap has important implications for clinical practice. Our review consolidates current evidence about how prescription medications affect post-lanosterol biosynthesis and outlines critical areas requiring urgent investigation.

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Introduction: Brain Sterol Biosynthesis is Critical for Normal Brain Development and Function

Cholesterol is essential for all mammalian cells, especially brain cells (1). The human brain accounts for approximately 2% of total body weight, yet it contains about 25% of cholesterol and cholesterol derivatives of the human body (2–4). The body's and the central nervous system (CNS) cholesterol pools are separated by the blood–brain barrier (BBB), each relying independently on its intrinsic cholesterol biosynthesis (5). Brain sterol biosynthesis starts during intrauterine development and continues throughout the patient's lifetime (5, 6). In an unesterified form, brain cholesterol is predominantly found in the myelin sheaths and plasma membranes of the various brain cells (2, 6).

Synapse and dendrite formation and axonal guidance are both sterol-dependent processes, and the sterol biosynthesis pathway generates dozens of bioactive molecules critical for normal brain function (7–11). Preserved cholesterol homeostasis is also necessary for regular functioning of the adult brain: in aging, high brain cholesterol has been connected to better memory function, while low cholesterol is associated with an increased risk for depression (12–14). In addition, disturbances in cholesterol biosynthesis and/or metabolism have been reported in Huntington's disease and Alzheimer's disease (15–17). Low cholesterol concentrations may predispose an individual to aggression, impulsivity, and violence (18–20).

Cholesterol Biosynthesis is a Complex Biochemical Process

Cholesterol is synthesized from acetyl-CoA in a long cascade of two final parallel chains of enzymatic events called the Kandutsch-Russell and Bloch pathways (Figure 1) (21). Conversion of the final sterol precursor, 7-dehydrocholesterol (7-DHC), to cholesterol is mediated by DHCR7 in the Kandutsch-Russell pathway (22). In the Bloch pathway, DHCR7 is necessary for the reduction of 7-dehydrodesmosterol (7-DHD) to desmosterol (DES) (23). Thus, disruption of DHCR7 function prevents normal cholesterol production through both post-lanosterol biosynthetic pathways and results in elevation of 7-DHC and 7-DHD and reduction in cholesterol and desmosterol levels (24).

7-DHC and 7-DHC–Derived Oxysterols have Strong Biological Effects

Reduced cholesterol production is detrimental to the brain, but the arising pathophysiology is more complex (25). As cholesterol precursors 7-DHC, 8-DHC, and 7-DHD accumulate (24, 26, 27), a new challenge emerges: 7-DHC is the most oxidizable lipid known to date, with a propagation rate constant of 2,160 (this is 200 times more than cholesterol and 10 times more than arachidonic acid) (28, 29). As a result, 7-DHC spontaneously oxidizes, generating highly reactive 7-DHC–derived oxysterols (30), impairing cell viability, differentiation, and growth (31, 32). The most investigated 7-DHC–derived oxysterol, DHCEO, interferes with neuronal morphology, neurite outgrowth, and fasciculation (31, 33). Furthermore, 7-DHC–derived oxysterols are simultaneously markers of oxidative stress (34) and biologically active molecules that modify immune function (33, 35). 7-DHD and 8-DHC, while much less studied, are also likely to generate their own oxysterols, as they have a comparable peroxidation rate to 7-DHC (29).

Pathogenic Variants in Sterol Biosynthesis Genes Result in Developmental Disabilities

While a complete lack of cholesterol biosynthesis is incompatible with life, partial cholesterol production due to pathogenic variants in post-lanosterol genes results in complex developmental disabilities (36). Mutations in post-lanosterol biosynthesis are associated with Smith-Lemli-Opitz syndrome (SLOS) (mutations in DHCR7) (25), desmosterolosis (mutations in DHCR24) (37, 38), chondrodysplasia punctata 1 [mutations in emopamil binding protein (EBP)] (39, 40), and lathosterolosis (mutations in SC5D) (41). All these syndromes affect brain and craniofacial development and lead to intellectual and developmental disabilities (36, 42).

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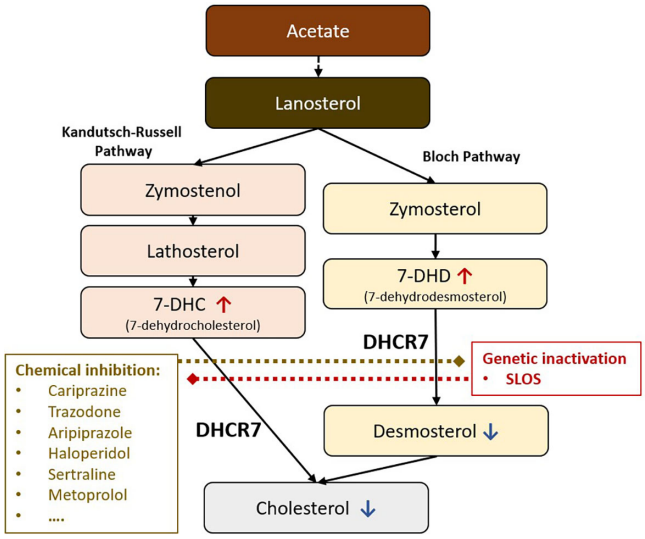

Figure 1. Commonly used prescription medications have a post-lanosterol biosynthesis inhibiting effect. Pathogenic variants in the DHCR7 gene result in SLOS with a hallmark sterol inhibition signature. This profile encompasses the accumulation of 7-DHC and 7-DHD and the reduction of desmosterol and cholesterol levels. Many commonly used prescription medications give rise to similar biochemical signatures and can be considered sterol biosynthesis inhibitors. The post-lanosterol pathway is greatly simplified for readability.

DHCR7 Inhibitors During Pregnancy are Considered Teratogens

Boland and Tatonetti published a systematic literature review in 2016, which revealed that first-trimester exposure to DHCR7 inhibitors met the criteria for teratogenicity. As a result, they suggested that DHCR7 activity should be considered during drug development and prenatal toxicity assessment (43).

Many Prescription Medications have Sterol Biosynthesis Inhibiting Side Effects

While cholesterol and post-lanosterol intermediates do not cross the BBB, many prescription medications do so easily (44). These medications, designed for unrelated primary indications, can interfere with developmental brain sterol biosynthesis (45–51). Some medicines might directly inhibit key enzymes involved in sterol biosynthesis, while others could interfere with biosynthesis by altering gene expression, affecting the availability of substrates, or disrupting regulatory pathways (51). Regardless of the specific mechanisms involved, the consequences of disrupted sterol homeostasis can impact normal brain function in either case.

To date, over 30 prescription medications have been described as having post-lanosterol biosynthesis inhibiting side effects (52, 53). Aripiprazole, cariprazine, trazodone, and haloperidol have been the most extensively studied regarding their effects on sterol biosynthesis (46, 48, 54, 55). While they do not have a high degree of structural similarity or mechanism of action (except aripiprazole and cariprazine), they share a common biochemical signature and are all CNS-targeting medications. They are all DCHR7 inhibitors during development with a chemical signature that includes elevation of 7-DHC, 8-DHC, and 7-DHD and decreased desmosterol and cholesterol (52). These findings have also been validated across *in vitro* systems (52, 53, 56), rodent experiments and tissue types (45, 46, 48, 49), and analyses of blood samples from psychiatric patients and women of reproductive age (47, 54).

Single-Allele DHCR7 Pathogenic Variants Represent a Latent Vulnerability

Rodent transgenic models and in vitro human fibroblast cultures suggest that the DHCR7 genotype matters regarding the magnitude of sterol inhibition (54). Pathogenic variants of the *DHCR7* gene, present in approximately 1%–3% of the human population (57, 58), might not be sufficient to produce a disease but represent a latent vulnerability. More than 200 likely pathogenic variants of DHCR7 have been identified to date (59, 60). While the exact pathogenic variants might vary in frequency across different populations, the overall frequency of vulnerability appears to be comparable across sex and ethnic groups, with perhaps the exception of East Asian and Korean populations (0.5%–1%) (61). DHCR7± individuals have increased baseline 7-DHC levels. When their human fibroblasts are exposed to medications with sterol-inhibiting side effects, the sterol biosynthesis disruption reaches a magnitude close to that seen in patients with SLOS (50, 54). Rodent transgenic findings on Dhcr7± mice also confirmed these findings, providing additional insights into the potential underlying pathophysiology. Namely, a maternal exposure model revealed that both maternal and offspring Dhcr7± heterozygosity conferred vulnerability: Dhcr7± pups born to Dhcr7± mothers showed the highest sterol biosynthesis disruption in repose to aripiprazole, trazodone, and cariprazine (45, 46, 48). Thus, it appears that, at least in experimental systems, genetic vulnerability and chemical inhibition synergize, with yet unknown consequences on human health. The mechanism by which this gene–medication interaction occurs remains unknown, and this might be different for the various compounds that can inhibit sterol biosynthesis. Namely, while the pathogenic genetic variant will reduce the availability of the DHCR7 enzyme, the medications can either directly inhibit the same enzyme, inhibit another upstream enzyme in the post-lanosterol biosynthesis pathway, or interfere with genes belonging to networks responsible for sterol enzyme biosynthesis, degradation, or turnover. Ultimately, elevated 7-DHC and related oxysterol levels have substantial biological activities, including inhibiting Hedgehog response (62, 63), a key driver of normal brain development. Similarly, the p75 neurotrophin receptor expression depends on the cholesterol biosynthesis machinery (64).

Sterol Biosynthesis Inhibiting Polypharmacy Effects are Synergistic or Summative

We live in the age of polypharmacy, a nationwide and worldwide challenge (65–67). Polypharmacy is increasingly common in the United States and contributes to the substantial burden of drug-related morbidity. Quinn and Shah counted the incidence of multidrug combinations observed in 4 billion patient-months of outpatient prescription drug claims from 2007–2014 in the Truven Health MarketScan Databases (65). They found that among patients taking any prescription drug, half were exposed to two or more drugs, while 5% were exposed to eight or more. Notably, CNS polypharmacy is particularly commonly seen in the treatment of mental illness (68).

If genetic Dhcr7± vulnerability and chemical inhibition of sterol biosynthesis synergize, could two or more medications with sterol-inhibiting side effects have a similar, synergistic, or summative effect? In vitro, rodent, and human biomaterial studies suggest this might be the case (69, 70). Neuronal and astrocytic cultures treated with ARI+TRZ showed an additive effect, increasing the 7-DHC/CHOL ratio by 15- to 20-fold over vehicle-treated cultures. In addition, adult mice treated with ARI+TRZ polypharmacy affected multiple organ systems of the body, leading to decreased proliferation and reduction of neural progenitor cells in the hippocampi of male adult mice and decreased expression of microglial marker IBA1 in the brain (69, 70). Furthermore, in a study of pregnant women taking prescription medications, it was reported that women taking more than one medication with 7-DHC–elevating side effects had the highest 7-DHC levels in their blood, suggesting a synergistic or summative effect of polypharmacy (47).

This raises the question of when and where will the polypharmacy effects summate or synergize. The drugs that show synergy have different mechanisms of action, most commonly mediated through a specific receptor. If at least one medication's inhibition of post-lanosterol enzymes is receptor-based (and not direct chemical inhibition), the overlapping receptor distribution will define the site of most substantial synergy. In the case of nonoverlapping receptor distribution, synergy or summations would not be observed; instead, it would affect a broader tissue distribution where either one of the receptors is expressed. This could give rise to a very different phenotype and suggest that each combination of polypharmacy could have different ultimate consequences. Should this be the case, this would be further complicated by the developmental

timing of receptor expression vs. the timing of polypharmacy. Thus, the same combination of sterol-inhibiting polypharmacy could differently affect different organs, regions, or cell types based on their dose, timing of polypharmacy, receptor expression pattern, mechanism of action, developmental stage, genotype, and many other factors.

There are Likely to be Multiple Developmental Vulnerability Periods to Post-Lanosterol Inhibition

The vast majority of post-lanosterol inhibition data obtained to date has focused on intrauterine development and maternal intake of medications during pregnancy. However, many infants might be potentially treated with (known or yet unknown) medications that could inhibit sterol biosynthesis. Early postnatal development is also likely to be a critical vulnerability window (71) as this is a period of progressive myelination and development of glial cells, both highly sterol-dependent processes. Furthermore, puberty is a period of rapidly changing hormonal homeostasis, synaptic pruning, and continued myelination, all strongly influenced by sterol biosynthesis (72, 73). This is also a period where physicians are more likely to prescribe medications with sterol-inhibiting side effects. The overall and specific medication effects causing partial sterol inhibition are almost entirely unknown in these postnatal vulnerability periods. Yet, the detrimental effects of post-lanosterol inhibition would not result in dysmorphologies seen during fetal development but could have functional consequences. Namely, interference with myelination and synaptic pruning, both sterol biosynthesis-dependent processes, could result in changes in functional connectivity. Such disruptions would ultimately result in learning difficulties, emotional disturbances, developmental delay, language acquisition challenges, or behavioral alterations.

Differential Effects of *DHCR7* Inhibition in Tissue and Cell Types

While representing only 2% of body weight, the brain contains 25% of the body's cholesterol and sterol derivatives. However, brain sterol biosynthesis is not homogenous across brain regions. For example, cholesterol in the pons and cerebellum is ~2.5 times higher than in the neocortex (74). Furthermore, *in situ* hybridization for post-lanosterol biosynthesis enzymes reveals markedly different expression levels across cell types, with very high expression in the principal neurons of the hippocampus (64) and serotoninergic cells. This later is also underscored by a functional vulnerability of *Dhcr7*± mice, revealing an increased head-twitch response to the 5-HT2A agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (75). These findings have several potentially significant implications. First, the brain is likely the most sensitive organ to developmental sterol inhibition. Second, it is likely that brain regions that have the highest enzyme expression and sterol production are the most likely affected by sterol inhibition. Third, as developmental sterol accumulation proceeds differently across the different brain regions, the same sterol-inhibiting medication, given at other times, might affect different brain structures. Fourth, high 7-DHC levels are likely to affect the various brain cell types differently, perhaps regulated by their neurochemical content. Finally, when discussing the effects of post-lanosterol biosynthesis disruption, one must consider that sterols might be synthesized in one cell or region. Still, they are also actively trafficked to all parts of the brain and interchanged between glial and neuronal cells (76).

There is Still a Significant Amount of Critical Knowledge Missing

While there is plenty of evidence suggesting a cautionary approach when using medications with sterol-inhibiting side effects during pregnancy, there are significant gaps in our current data.

1. We have limited knowledge of how these medications interfere with developmental sterol biosynthesis. The mechanism might be direct inhibition of the enzyme(s) or receptor-mediated, and such information would be essential to obtain.
2. While we understand that DHCR7 single allele pathogenic variants might potentiate the effects of sterol inhibiting effects, such synergy has not yet been investigated for single copy pathogenic alleles in genes encoding other post-lanosterol enzymes (e.g., DHCR14 or EBP).
3. We do not understand the effects of elevated 8-DHC and 7-DHD and their oxysterols. Based on their chemical structure and properties, they are very likely to be abundant and biologically active, but no such information is available to date (29).
4. The exact time window of a potential developmental vulnerability remains unknown, as is the dose and duration of medications that could cause potential harm.
5. We do not know whether there is a critical threshold or concentration of 7-DHC (or oxysterols) that becomes harmful to the developing baby's brain or other tissue (31).
6. Can co-morbidities also synergize with medication-induced inhibition of sterol biosynthesis, like polypharmacy and Dhcr7 genotype? Diabetes, pre-eclampsia, metabolic conditions, and lifestyle factors could theoretically make the developmental outcomes of sterol inhibition much worse.
7. We are exposed to hundreds of chemicals throughout our daily lives, and some of them have sterol inhibition properties (51, 53, 77, 78). Do these chemicals predispose to developmental disabilities, in particular, if they are combined with the already identified sterol-inhibiting genetic factors or prescription medications?
8. Commonly used medications can potentially inhibit other enzymes in the post-lanosterol biosynthesis pathway (51). For example, amiodarone alters cholesterol biosynthesis through the inhibition of EBP and dehydrocholesterol reductase 24 (DHCR24), both of them post-lanosterol enzymes (79). Yet, this is a greatly understudied area.
9. A recently identified Fetal Fentanyl syndrome (FFS) (80) arising in newborns born to mothers with nonprescription fentanyl use has a remarkable phenotypic and biochemical similarity to SLOS. This suggests that FFS partially arises from sterol inhibition (81). Furthermore, a recent review found that 10 of 12 case-control and 7 of 18 cohort studies documented statistically significant positive associations between maternal opioid use during pregnancy and congenital malformations (82). Are these dysmorphologies a result of sterol biosynthesis inhibition, or are they arising through an unrelated mechanism (83)?
10. Are there deleterious consequences of long-term use of medications with sterol-inhibiting side effects for adults? Low cholesterol levels appear to be associated with an increased risk for depression (84, 85, 13, 12). Furthermore, a recent study evaluating interactions between antipsychotics and medications used in the treatment of cardiovascular disease reported the highest number of interactions among beta-blockers and antipsychotics (66). Remarkably, the combinations that reported the most common adverse outcomes included the medications that have been previously identified as having 7-DHC–elevating side effects – including metoprolol and nebivolol (49).

Potential Clinical Implications and Recommendations for Policies and Future Research

Based on the above-presented cautionary findings, we believe that in clinical practice, several approaches are warranted:

- Pregnant mothers with *DHC7*± genotype should not be utilizing medications with 7-DHC–elevating side effects. There are usually safe alternatives to these medications, so this approach should rarely interfere with the best patient treatment.
- We recommend genetic testing of pregnant women who must utilize medications with sterol-inhibiting side effects. If prenatal testing is also performed, it is imperative to gain insight into the *DCHR7* status of the unborn child. This is especially important when the unborn child and mother carry single-allele *DCHR7*± pathogenic variants, as these babies might be the most vulnerable to post-lanosterol biosynthesis disruptions.
- Patients with SLOS should never receive medications with 7-DHC–elevating side effects.
- Clinicians should be educated about the potential danger of medications with DCHR7-inhibiting side effects for the developing brain. During pregnancy (and potentially during other vulnerability periods), they should avoid prescribing polypharmacy that shows potential synergistic interaction on the post-lanosterol biosynthetic pathways. It is rarely appreciated that 7-DHC–elevating medications might target

different organ systems (e.g., psychotropic and cardiac medications – trazodone + metoprolol), yet their unwanted effects might converge on the same biochemical pathway.

National regulatory organizations should pay close attention to all the above-listed findings and develop or revise knowledge-based guidelines for utilizing such mediations. Furthermore, pharmaceutical companies should routinely assess newly developed (and perhaps already approved) medications for their effects on developmental sterol biosynthesis. In addition, national funding agencies should invest in research to find definitive answers to these essential public health questions. With the rapid emergence of new technologies such as *in situ* metabolomics and lipidomics (74, 86), bioinformatics, new model systems [including induced pluripotent stem cells (iPSCs) (87) and humanized mice], and novel, high-resolution imaging technologies, we should be able to gain a more definitive insight in the risk-reward equation for each medication and develop a safe, personalized treatment plan for our patients.

Conclusions

Unintended sterol inhibition by many prescription medications is well documented, and it is a potential cause for concern when used during pregnancy. Nevertheless, it should be acknowledged that many of the findings presented above are obtained using in vitro and transgenic rodent models. While the post-lanosterol biosynthetic pathway is highly conserved between rodents and humans, it is uncertain which of those findings translate to the human population. For each individual, the magnitude of sterol disruption (and potential consequences for the unborn child) will likely depend on lifestyle, dosage, potential polypharmacy, genetic makeup, and other possible factors. Nevertheless, the above-presented data advises caution and a conservative approach in the use of medications with sterol-inhibiting side effects during pregnancy.

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Author Contributions

K.M. and Z.K. obtained many of the presented results, discussed the findings, and wrote the manuscript together. Both authors have read and approved the manuscript. The authors take full responsibility for all data, figures, and text and approve the content and submission of the study. No related work is under consideration elsewhere. Corresponding author: Prof. Mirnics for all aspects of the presented work.

Author Disclosures

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THOUGHT LEADERS INVITED REVIEW

CD2AP in Alzheimer's disease: Key mechanisms and therapeutic potential

Yong Wang[1], and Yun-wu Zhang[1]

Alzheimer's disease affects millions worldwide as one of the most devastating neurodegenerative conditions, characterized by two distinct pathological features: amyloid plaques (composed of clustered β-amyloid peptides) and neurofibrillary tangles (made of hyperphosphorylated Tau protein). These hallmark changes trigger a cascade of events, including progressive synaptic dysfunction, inflammation, and the breakdown of the protective blood–brain barrier. Recent breakthrough research through genome-wide association studies has identified CD2-associated protein (CD2AP) as a significant risk factor in developing Alzheimer's disease, with this crucial adaptor protein emerging as a key player in several disease mechanisms due to its fundamental role in cellular transport and cytoskeletal architecture. Growing evidence reveals that CD2AP influences multiple aspects of Alzheimer's disease pathogenesis, from β-amyloid metabolism and deposition to Tau-mediated neurotoxicity, synaptic integrity, blood–brain barrier function, and microglial activation states. Understanding CD2AP's physiological and pathological roles in the nervous system, particularly its cell type-specific functions, is crucial for developing effective therapeutic strategies that target CD2AP levels for Alzheimer's prevention and treatment, requiring a comprehensive understanding of CD2AP biology in neuronal cells.

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by impairments in cognitive functions, especially in learning and memory. The primary pathological features observed in the brain tissues of deceased patients with AD include extracellular amyloid plaques composed of β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated Tau proteins (1). Due to an aging society worldwide, the number and proportion of people with AD or other dementias are expected to grow in the coming years. In 2019, some 55 million people were estimated to have dementia across the world, a figure predicted to increase to 139 million by 2050, according to the WHO. The annual cost of dementia was estimated to be US $1.3 trillion in 2019, with this figure expected to more than double by 2030 to $2.8 trillion (2).

AD can be classified into early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD) based on the age of onset (before or after 65 years old), with EOAD accounting for 5%–10% of the incidence (3). Studies indicate that EOAD is often linked to familial genetic mutations, particularly in the genes encoding β-amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2) (4, 5). In contrast, the majority of LOAD cases are typically sporadic and associated with multiple factors, including environmental influences. Since the identification in 1993 of the Apolipoprotein E (APOE) ε4 allele as a significant genetic risk factor for LOAD (6, 7), genome-wide association studies (GWAS) have uncovered additional genes related to LOAD, such as *TREM2*, *BIN1*, *MS4A4*, *CD33,* and *CD2AP* (8–10). *CD2AP* encodes CD2-associated protein (CD2AP), also referred to as Cas ligand with multiple SH3 domains (CMS) (8–11). In this article, we provide a concise review on the latest research advancements concerning the functional role of CD2AP in AD.

CD2AP Introduction

The human *CD2AP* gene is located on chromosome 6 and comprises 18 exons (Figure 1A). It encodes a protein consisting of 639 amino acids with a molecular weight of approximately 71 kDa. The mouse *Cd2ap* gene is located on chromosome 17 and contains 18 exons, encoding a protein of 637 amino acids. The CD2AP protein is a scaffold protein that was initially identified due to its interaction with the transmembrane protein CD2 in T cells. This interaction facilitates CD2 clustering and stabilizes the connection between T cells and antigen-presenting cells, leading to its naming in 1998 (12).

CD2AP is primarily composed of three consecutive SH3 domains near the N-terminus, a proline-rich region in the middle, and a coiled-coil domain at the C-terminus [Figure 1A, with the three-dimensional structure of CD2AP derived from AlphaFold 3 (13, 14)]. The SH3 domains of CD2AP specifically recognize target protein sequences composed of extended polyproline type II helices. They are essential for CD2AP interaction with various cellular components, including cytoskeletal regulators, multiple signaling molecules, and apoptosis regulatory factors (15–17). The central proline-rich region of CD2AP mediates ligand-dependent interactions with actin-binding proteins, facilitating their recruitment to endocytic CD2AP-Cbl-epidermal growth factor receptor complexes (18). The C-terminal coiled-coil domain of CD2AP is indispensable for its actin-binding capability, as this region contains a conserved sequence of approximately 20 residues, known as the CARMIL peptide that specifically interacts with actin-capping protein (CP). This interaction enables CP to bind to the barbed ends of actin filaments, thereby capping the filaments and regulating actin monomer addition and loss. Furthermore, the C-terminal region of CD2AP contains specific binding sites for membrane proteins such as nephrin and podocin, highlighting its multifunctional role in cellular processes (19–23).

CD2AP is expressed throughout the body, with relatively high levels in the stomach, duodenum, colon, and kidneys. CD2AP is particularly enriched in podocytes of the glomeruli (24). In glomerular cells, CD2AP plays a crucial role by interacting with proteins such as nephrin and podocin at the slit diaphragm, anchoring these proteins to the actin cytoskeleton. This interaction is essential for maintaining the function of podocytes and the slit diaphragm during the glomerular filtration process (25, 26). CD2AP is indispensable for normal glomerular function. Mice with a complete knockout of the *Cd2ap* gene exhibit progressive glomerular dysfunction due to the loss of podocyte foot process integrity and typically die of renal failure within 6 to 7 weeks after birth (27).

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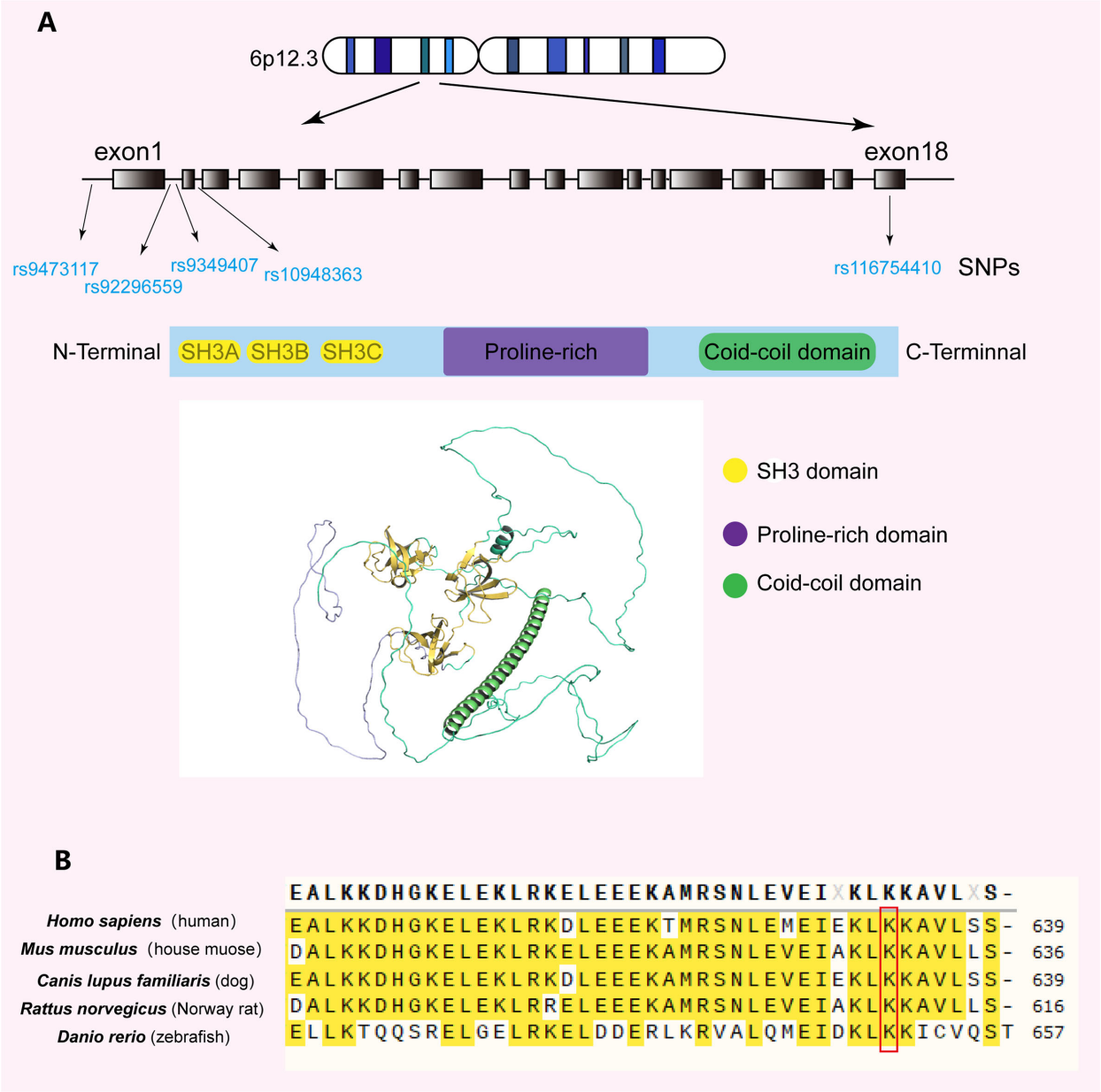

Figure 1. The scheme of CD2AP. (A) Human *CD2AP* gene and CD2AP protein. The *CD2AP* gene is located on chromosome 6p12.3 and has 18 exons. The CD2AP protein contains three SH3 domains, a proline-rich domain and a coil-coil domain. The three-dimensional structure of CD2AP is derived from AlphaFold 3. SNPs associated with AD are listed. (B) Comparison of CD2AP sequences of different species around K633 (highlighted by a red box).

CD2AP also participates in tumor growth but shows diverse effects in different cancers. For example, CD2AP was found to display a specific expression pattern in human urogenital organs but with distinct expression patterns in several types of kidney tumors (28). Another study revealed a reduction of CD2AP expression in renal clear cell carcinoma (ccRCC) and an association of lower CD2AP expression level with worse patient prognosis, implicating that CD2AP may be a prognostic biomarker for ccRCC (29). In addition, CD2AP was found to form a scaffold protein complex with TKS4 for regulating the migration and epithelial-mesenchymal transition pathways of HCT116 colon cancer cells (30). Furthermore, CD2AP could promote cell adhesion and influence cytoskeletal assembly by interacting with the protein CAPZA1, thereby regulating the metastasis of gastric cancer cells (31). Recently, we also revealed that CD2AP was upregulated in glioblastoma, in which CD2AP could enhance the NF-κB signaling by interacting with TRIM5, thereby promoting the malignant behavior of glioblastoma (32).

Since the identification of the association between CD2AP and AD, the function of CD2AP in the brain has been attracting more and more attention. The mRNA data from the Allen Brain Atlas suggest that although CD2AP may be expressed at low levels in neurons, it is relatively enriched in highly plastic brain regions such as the hippocampus, cortex, and cerebellum (33, 34). In addition, high expression of CD2AP was observed in dendritic endosomes of primary cultured mouse neurons (34). Since neurons share morphological similarities with podocytes, as both possess abundant actin-rich projections and have common actin regulators such as synaptopodin and cortactin (35), CD2AP might play a significant role in neurons as it does in podocytes. Indeed, the absence of CD2AP in neurons was shown to cause synaptic damage (36–38). Moreover, we recently discovered that CD2AP was expressed at higher levels in microglia compared to neurons in mice and that CD2AP could regulate microglial activation in response to Aβ toxicity (39). These findings indicate that CD2AP also plays a critical role in the central nervous system.

Relationship Between CD2AP and AD

CD2AP Single-Nucleotide Polymorphisms Are Associated with AD

In 2011, Naj *et al.* and Hollingworth *et al.* independently conducted genome-wide association studies (GWAS) using large samples and consistently identified that the single-nucleotide polymorphism (SNP) rs9349407 in *CD2AP* intron 1 significantly associated with LOAD (8, 9). Subsequent replicative studies reported controversial results on the association between rs9349407 and AD, with both positive (40–42) and negative (43–46) correlations suggested. However, most negative studies used relatively small sample sizes. Another work studying deceased individuals who underwent complete neuropathological evaluations found that the rs9349407 locus was related to neuritic plaque pathology (47).

The work by Hollingworth *et al.* further identified that the SNP rs9296559 in *CD2AP* intron 1 was also associated with LOAD (9), and this association was confirmed in the southern Han Chinese population (42). Other studies identified additional SNPs in the *CD2AP* gene to associate with AD, such as rs10948363 in *CD2AP* intron 2 (48, 49) and rs116754410 in *CD2AP* exon 18 (50), of which the latter results in a missense mutation (K633R) in CD2AP. The amino acid K633 is located in the coiled-coil domain of CD2AP, and one recent study found that CD2AP K633R overexpression in neurons could increase spine density and volume. In contrast, its overexpression failed to rescue impaired spine density in CD2AP-deficient neurons (37). Herein, we also evaluated the conservation of K633 and found it conserved from humans to zebrafish (Figure 1B), further implicating the importance of K633 for CD2AP function; this requires further investigation. Moreover, The SNP rs9473117 located upstream of *CD2AP* was reported to be associated with EOAD (51).

CD2AP Expression Alteration in AD

It was reported that *CD2AP* expression decreased in peripheral blood lymphocytes in patients with LOAD (42). However, we recently noticed that in one proteomic study with large datasets (52), CD2AP protein levels were significantly increased in the brain of patients with AD compared to control subjects and asymptomatic patients with AD (39). We also found that CD2AP levels significantly increased in the hippocampus of the 5xFAD AD model mice at pathological stages but not at pre-pathological stages, and such an increase probably occurred specifically in microglia (39). Our findings implicate that CD2AP alterations in AD occur after pathological changes. Consistent with our results, an earlier study also reported that CD2AP levels were increased in the brain of the APP/PS1 AD model mice (53).

Although several SNPs around *CD2AP* have been reported to be highly associated with AD, only a few studies have explored the effects of some of these SNPs on *CD2AP* expression so far. In a study analyzing human brain gene expression data, researchers found that the minor allele of rs9349407 was only associated with decreased *CD2AP* expression in the cerebellar cortex (54). While the study showed that rs9473117 associates with EOAD, the minor allele of rs9473117 was found to associate with increased *CD2AP* expression in the thalamus and cerebellar cortex (51). In addition, Pavešković *et al.* leveraged new paired single-nucleus RNA-sequence and whole genome sequencing data and found that the risk variant of rs9473117, together with those of rs7767350 and rs9369716 that are in strong linkage disequilibrium with rs9473117, increases human *CD2AP* mRNA expression in both excitatory and inhibitory neurons, as well as in microglia (36).

CD2AP Regulates APP Transport and Aβ Production

One major pathological feature of AD is the formation of amyloid plaques composed of Aβ, which is derived from APP through sequential cleavages. First, APP is cleaved by the β-secretase (BACE1) to generate soluble extracellular APP (sAPPβ) and a C-terminal fragment (CTFβ). APP CTFβ is then cleaved by the γ-secretase to produce Aβ fragments of 40 or 42 amino acids in length, namely Aβ40 and Aβ42 (55, 56). The cleavage of APP is determined by the subcellular localization of APP and its interactions with BACE1 and γ-secretase during membrane, endosome, and lysosome trafficking (57, 58).

CD2AP is an actin-associated adaptor protein that, along with several members of the Rab family, participates in the docking process of vesicles to target membranes and regulates endosome morphology (19). Several studies have suggested that CD2AP is involved in the intracellular transport and cleavage of APP for Aβ production. Furusawa *et al.* found that overexpression of CD2AP at the cellular level accelerated the transport of APP from early endosomes to late endosomes, thus initiating the degradation process of APP without affecting its degradation rate. In contrast, knocking down CD2AP in cells significantly increased intracellular APP levels (59). Ubelmann *et al.* also showed that CD2AP could keep APP and BACE1 apart in early endosomes in neurons: CD2AP deficiency increased the trapping of APP at the limiting membrane of early endosomes and thus reduced its sorting for degradation in dendrites so that APP and BACE1 had elevated convergence in early endosomes for increased Aβ generation (34). However, Liao *et al.* reported that in the N2a-APP695 cell line, overexpressing APP, knocking down CD2AP reduced cell membrane APP levels and Aβ release and lowered the Aβ42/Aβ40 ratio. Moreover, they found that in 1-month-old APP/PS1 mice with complete loss of CD2AP, the Aβ42/Aβ40 ratio was decreased. While, CD2AP haploinsufficiency had no effect on Aβ deposition up to 7 months of age in APP/PS1 mice (60). One recent study also reported that in APP/PS1 mice with neuron-specific CD2AP knockout, Aβ levels were not altered at 4.5 months of age (61). Due to the inconsistency in different studies, the specific role of CD2AP in APP processing and Aβ requires further in-depth investigation. Table 1 summarizes reported studies on the effects of CD2AP on APP trafficking/Aβ generation and other AD-related processes.

CD2AP Modulates Tau-mediated Neurotoxicity

Neurofibrillary tangles formed by hyperphosphorylated Tau protein represent another important pathological feature of AD. In one study using immunohistochemical assays to explore the association between CD2AP expression and AD pathologies in postmortem human brain samples, CD2AP was found not associated with Aβ deposits in vessels or parenchymal plaques. Instead, CD2AP immunodetection in neurons was positively associated with Braak neurofibrillary stage (62). Furthermore, the AD-associated *CD2AP* SNP rs10948363 was found to associate with NFTs (63), the AD-associated *CD2AP* SNP rs9349407 was found to associate with an increase in total Tau protein levels in cerebrospinal fluid, and the rs9381563 variant in *CD2AP* was correlated with changes in phosphorylated Tau levels in cerebrospinal fluid (64).

CD2AP also affects the neurotoxicity caused by Tau. In a fruit fly AD model expressing human Tau, researchers found that knockdown of the cindr gene (the human homolog of *CD2AP*) robustly enhanced Tau toxicity (65). Xue *et al.* also found that the specific knockout of CD2AP in neurons in APP/PS1 mice resulted in a significant increase in the phosphorylation levels of endogenous Tau protein. In contrast, the total Tau protein levels remained unchanged (61). Additionally, the deficiency of CD2AP led to elevated P38 phosphorylation levels in these mice. Treatment with P38 phosphorylation inhibitors attenuated the increased phosphorylation of endogenous Tau protein caused by the loss of CD2AP (61). It is known that P38 can phosphorylate Tau (66, 67). However, although some studies consistently reported that high glucose and TGFβ treatments decreased CD2AP while increased P38 phosphorylation (68, 69) and that CD2AP deficiency enhanced TGFβ-induced P38 activation (70), the precise mechanism by which CD2AP influences P38 phosphorylation remains unclear and deserves further scrutiny.

CD2AP Regulates Synaptic Growth and Development

Synapses are the core structures for signal transmission between neurons, and abnormalities in synaptic function are closely linked to cognitive impairment. In the early stages of AD, synaptic dysfunction appears, although the number of synapses does not significantly change at this stage. However, in the mid to late stages of AD, there is a significant loss of synapses and neuronal death, leading to a sharp decline in cognitive abilities (71–76). Ojelade *et al.* found that the cindr gene was involved in the development and maturation of synapses during the growth of fruit flies. Mutations in cindr disrupted the release and recycling of synaptic vesicles, impairing synaptic plasticity (38). They also noticed decreased levels of some synaptic proteins in CD2AP knockout mice (38). Additionally, they showed that cindr interacted with 14-3-3ζ to regulate the ubiquitin

Table 1. Current knowledge on the contribution of CD2AP to various AD-related processes

Study system	Findings	References
APP and Aβ		
Cells (HEK293, COS-7, N2a, neurons)	CD2AP overexpression enhances APP transport from early endosomes to late endosomes and APP degradation. CD2AP knockdown has opposite effects	(59)
Cells (N2a, neurons)	CD2AP knockdown stalls APP at the limiting membrane of early endosomes, increases the encounter of APP and BACE1, and promotes Aβ generation	(34)
N2a-APP695 cells	CD2AP knockdown reduces Aβ40 and Aβ42 and Aβ42/40 ratio, reduces cell surface levels of APP but not total APP	(60)
PS1APP mice with CD2AP KO	No significant change of Aβ40 and Aβ42, but decreased Aβ42/40 ratio in 1-month old mice	(60)
PS1APP mice with CD2AP haploinsufficiency	No significant change of Aβ40 and Aβ42 and Aβ plaques at 7 months old. Only decreased PBS-soluble Aβ42/40 ratio in 7-month-old female mice	(60)
APP/PS1 mice with neuron-specific CD2AP KO	Aβ not altered in 4.5-month-old mice.	(61)
Tau		
Flies expressing human Tau	CD2AP knockdown enhances Tau toxicity	(65)
APP/PS1 mice with neuron-specific CD2AP KO	Increased synaptic deficits and synaptic protein loss at 4.5 months old	(61)
Synapse		
Neurons	CD2AP knockdown reduces spine density and size and neuronal activity	(37)
Neurons	CD2AP knockout disrupts neuronal and synaptic morphology	(36)
Flies	CD2AP deficiency impairs synapse maturation and function	(38)
CD2AP KO mice	Decreased certain synaptic proteins at 5 months old	(38)
CD2AP heterozygous and homozygous KO mice	Abnormal pre-synaptic release with increased paired-pulse facilitation at 5 to 8 weeks old	(36)
CD2AP homozygous KO mice	Perturbation of proteins involved in synaptic function at 5 weeks old	(36)
5xFAD mice with microglial CD2AP haploinsufficiency	Improved synaptic damage at 7 months old	(39)
Microglia		
CD2AP-deficient microglia	Reduced phagocytosis ability	(39)
5xFAD mice with microglial CD2AP haploinsufficiency	Attenuated microgliosis at 7-months old	(39)
Blood–brain barrier (BBB)		
CD2AP KO mice with CD2AP transgene expression in the kidney	Compromised BBB integrity	(85)
Behaviors		
CD2AP heterozygous KO mice	Subtle impairments in discrimination learning at 2.5-months old	(36)
Nestin-Cre mediated brain CD2AP KO mice	No obvious cognitive and motor behavior changes at 3.5- and 12-months old	(36)
APP/PS1 mice with neuron-specific CD2AP KO	Accelerated cognitive deficit onset at 4.5-months old	(61)
5xFAD mice with microglial CD2AP haploinsufficiency	Improved cognitive behaviors at 7-months old	(39)
CD2AP KO mice with CD2AP transgene expression in the kidney	Normal behaviors	(85)

Abbreviation: KO, knockout.

proteasome system, thereby affecting the conversion of synaptophysin and plasma membrane calcium ATPase (PMCA); and the absence of cindr increased PMCA levels and decreased cytosolic calcium (38). Research by Mirfakhar *et al.* found that CD2AP knockdown in neurons resulted in decreased spine density and size and decreased neuronal activity (37). They also proposed that CD2AP controls the formation and growth of dendritic spines by regulating the balance of F-actin polymerization and depolymerization (37). Pavešković *et al.* also observed a marked reduction in the number of synapses and impaired synaptic plasticity in the hippocampus of CD2AP-deficient mice (36). In addition, CD2AP was suggested to regulate the length and complexity of neuronal axons and the number of filopodia at growth cones through coordinating nerve growth factor signaling (77). Moreover, we recently found that specific deletion of CD2AP in microglia attenuated synaptic damage in 5xFAD mice at pathological stages, though this is attributed to reduced synapse phagocytosis by CD2AP-deficient microglia (39). These findings collectively suggest that CD2AP plays a crucial role in synaptic development in neurons, and its alteration may contribute to synaptic dysfunction in AD. A summary of the regulation of APP, Tau, and synapses in neurons by CD2AP is illustrated in Figure 2.

CD2AP Regulates Microglial Activity

In addition to Aβ plaques and Tau tangles, AD is also characterized by neuroinflammation. Microglia are primary immune cells of the brain and are activated in response to toxicity to exert protective function during the early stages of AD. However, in the later stages of AD, excessively activated microglia can exacerbate disease progression by releasing toxic proinflammatory factors and phagocytosing functional synapses (78–81). CD2AP was initially discovered as a ligand for CD2 in T cells, implicating its significant role in immune cells (12). We recently found that CD2AP

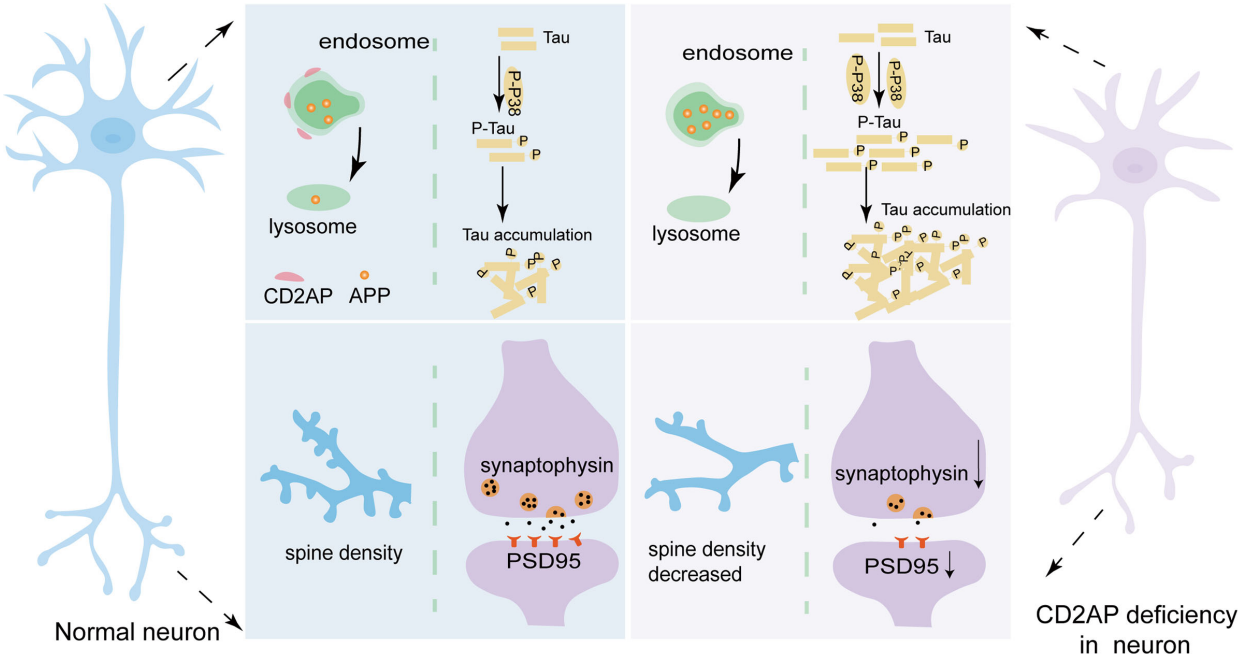

Figure 2. Impact of CD2AP function in neurons. CD2AP regulates APP transport from endosomes to lysosomes, Tau phosphorylation, and synapse formation and maintenance in neurons. CD2AP deficiency results in increased APP retention in endosomes for elevated Aβ generation, increased Tau phosphorylation and accumulation, and reduced synapse numbers and synaptic proteins such as synaptophysin and PSD95.

deficiency reduced microglial response to Aβ and microglial phagocytosis ability. Notably, we showed that in contrast to the deteriorating effect of neuronal knockout of CD2AP in APP/PS1 mice (61), microglial CD2AP deficiency attenuated cognitive defects, synaptic damage, and disease-associated microglia (DAM) in 5xFAD mice at pathological stages (39). We further suggested that one possibility for such a rescuing effect was that CD2AP could interact with the critical microglial survival factor, colony stimulating factor 1 receptor (CSF1R), so that CD2AP deficiency ameliorated the CSF1R signaling–mediated microglial activation and downstream expression of the C1q complement, which is crucial for synapse phagocytosis, and the formation of DAMs triggered by toxic Aβ (Figure 3) (39). The seemingly contradictory data regarding the effects of microglial CD2AP and neuronal CD2AP on Aβ pathologies are likely stem from distinct action mechanisms in each investigated cell type. However, it is also possible that they are caused by different experimental models used in these studies. However, so far, our understanding of the role of CD2AP in microglia and other cell types lags behind that in neurons. There are urgent requirements for elucidating the pathophysiological functions of CD2AP in different cell types and parallelly comparing their contributions to AD.

CD2AP Participates in the Integrity of the Blood–Brain Barrier

The blood–brain barrier (BBB) provides a physical barrier to protect the brain from harmful materials in the peripheral environment. The disruption of the BBB can lead to the influx of neurotoxic bloodborne debris, cells, and microbial pathogens into the brain, triggering inflammatory responses and related immune reactions, which may initiate various pathways leading to neurodegenerative diseases such as AD (82–84). MRI studies have shown that the BBB function is impaired in patients with early AD and other neurodegenerative diseases. Analyses of postmortem tissues of AD patient brain tissues also support this conclusion (82). Brain microvascular endothelial cells, which express high levels of CD2AP, are key components of the BBB (85). CD2AP homozygous knockout mice with CD2AP transgene expression in the kidney attenuated their mortality rate. Such mice showed overall normal behaviors. However, they had compromised the integrity of the BBB so intraperitoneally administered pentylenetetrazol increasingly penetrated into the brain to induce seizures in much shorter latency periods in these mice than in controls (85). This finding implicates that abnormal expression of CD2AP in brain microvascular endothelial cells, if any, may lead to BBB dysfunction and facilitate AD progression.

Conclusion

CD2AP is intricately involved in intracellular protein transport and degradation, vesicle trafficking, cell signaling, and cytoskeleton remodeling. As a risk factor for AD, abnormalities in CD2AP in the nervous system may contribute to the pathogenesis of AD through various mechanisms, including influencing the transport and processing of APP and thus Aβ generation, participating in Tau-mediated neurotoxicity, disrupting synaptic function and vesicle release, modulating microglial activation, and compromising the integrity of the BBB. However, the specific molecular mechanisms by which CD2AP participates in these processes have yet to be fully elucidated. Moreover, CD2AP in different neural cell types may have contradictory effects on AD pathologies. Further detailed research into the pathophysiological roles of CD2AP in the nervous system, especially in various cell types, will provide new insights into the pathogenesis of AD. With a comprehensive understanding of the exact pathophysiological functions of CD2AP in different neural cells, it is also possible to design cell type–specific drugs to promote CD2AP levels in those whose CD2AP deficiency is pathogenic (e.g., neurons) and to reduce CD2AP levels in those whose CD2AP elevation is pathogenic (e.g., microglia) as potential therapeutic approaches for AD.

Author Contributions

Y.W. wrote a draft. Y.-w.Z. reviewed and revised the manuscript.

All authors have read and approved the manuscript. All authors take full responsibility for all data, figures, and text and approve the study's content and submission. No related work is under consideration elsewhere. All authors state that all unprocessed data are available, and all figures accurately present the original data.

Corresponding author: Professor YwZ for any aspect of the work. This corresponding author takes full responsibility for the submission process.

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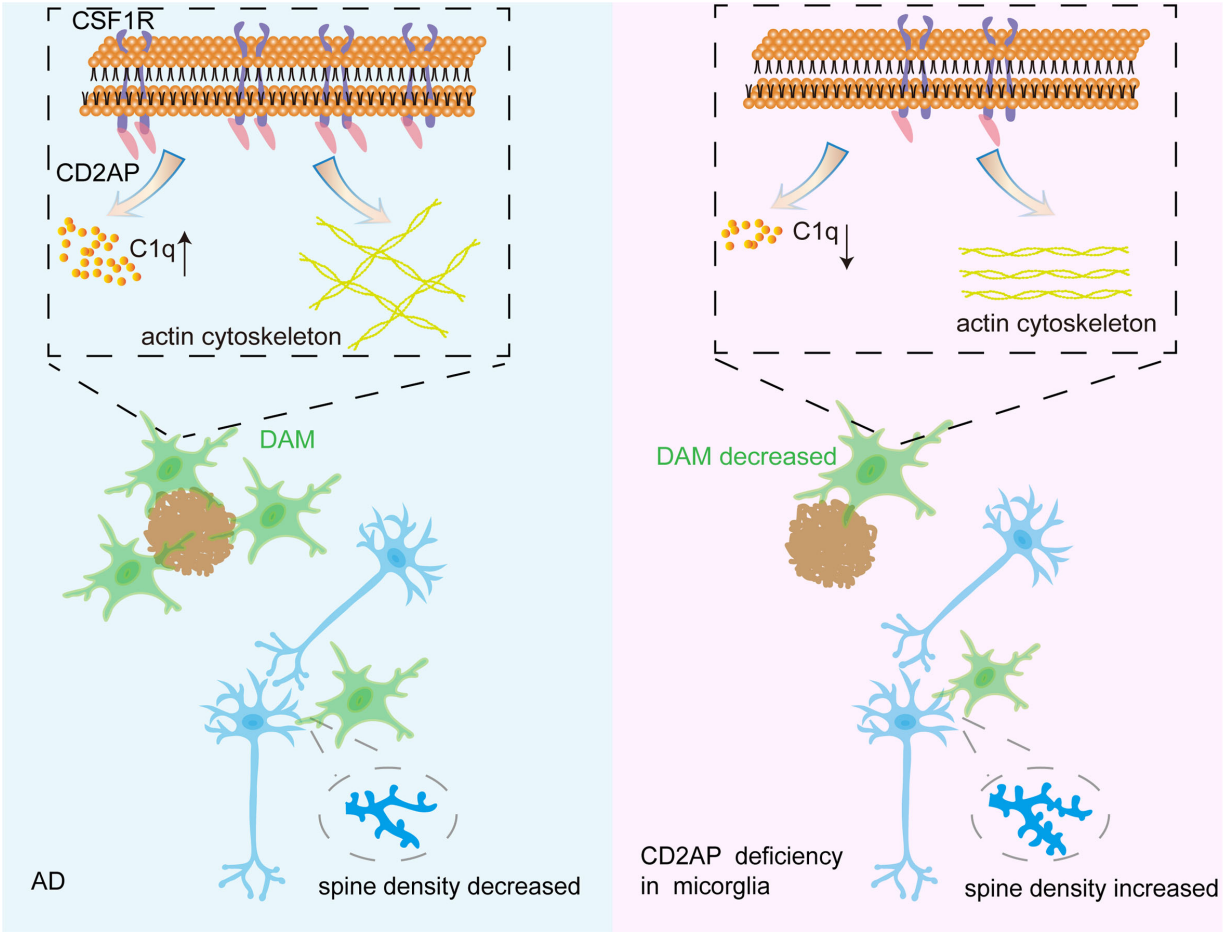

Figure 3. Impact of CD2AP deficiency in microglia in AD. Microglial CD2AP levels are increased in AD, leading to elevated CSF1R signaling and C1q expression and cytoskeleton remodeling in microglia, resulting in the formation of disease-associated microglia (DAM) and elevated microglial phagocytosis of synapses. CD2AP deficiency in microglia attenuated these changes to protect against AD.

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Author Disclosures

The authors have confirmed that no conflict of interest exists.

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RESEARCH ARTICLE

Maternal immune activation impairs hippocampal pyramidal neuron excitability in newborn rat offspring: Implications for neurodevelopmental disorders

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Maternal infection during pregnancy is associated with an increased risk of neurodevelopmental disorders, including depression, schizophrenia, and autism spectrum disorder. The hippocampus plays a critical role in these disorders, but the impact of maternal immune activation (MIA) on early hippocampal neuron function remains poorly understood. We investigated the effects of lipopolysaccharide-induced MIA in pregnant rats (20–80 μg/kg on gestational days 15–19) on the electrophysiological properties of hippocampal pyramidal neurons from newborn offspring. Primary neuronal cultures were prepared from the hippocampi of newborn rats and maintained for 13 days in vitro (DIV13). Whole-cell patch-clamp recordings assessed neuronal excitability parameters between DIV4-13. MIA significantly altered action potential characteristics in offspring hippocampal neurons, including: (1) increased latency time, threshold potential, and repolarization potential; (2) decreased peak potential, ascend and descend velocities; and (3) reduced spontaneous and evoked firing frequencies. These alterations suggest impaired glutamatergic neurotransmission in the hippocampus of MIA offspring, with potential sex-specific effects observed for spontaneous activity. Our findings demonstrate that MIA significantly decreases the excitability of hippocampal pyramidal neurons in newborn offspring. This reduced glutamatergic neurotransmission may contribute to the pathophysiology of neurodevelopmental disorders associated with maternal infection during pregnancy. This study provides novel insights into early neurophysiological changes following prenatal immune challenge that may inform therapeutic interventions targeting hippocampal function.

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Keywords: Electrophysiology, glutamate, hippocampus, lipopolysaccharide, maternal immune activation, neurodevelopmental disorders, neuronal excitability

Introduction

The recent COVID-19 pandemic demonstrated that our civilization is more vulnerable to acute infectious diseases than it was thought before. Since acute contagious diseases are not avoiding pregnant women, the investigation of long-term consequences of maternal infection on the offspring is strongly needed. It has been reported that the children of women suffering from an acute infectious disease during pregnancy were found to have a higher risk of future development of depression (1), schizophrenia (2–6), and autism (7). However, knowledge of the mechanisms mediating the neurodevelopmental effects of maternal infectious illness is limited.

An acute infectious illness increases blood concentrations of inflammatory and anti-inflammatory cytokines and stress hormones, such as corticosteroids. These factors can pass the placenta, as well as the blood–brain barrier, and affect embryonal neurodevelopment. Studies in laboratory animals involving maternal immune activation (MIA) with a bacterial (lipopolysaccharide or LPS) (8) or viral (polyinosinic: polycytidylic acid or Poly I:C) (9) antigens showed that the MIA primarily affected central serotonergic (5-HT) and dopaminergic pathways, as well as the hippocampus.

Our previous study showed that the MIA with LPS altered the rates of the spontaneous firing activity of central 5-HT and dopamine-secreting neurons in offspring in a sex-dependent way. The former was decreased in both sexes, and the latter increased in males only (8). Similar effects on the excitability pattern of dopaminergic neurons were observed after the MIA with immune activation by Poly I:C (9). Offspring of LPS-treated dams had also lower 5-HT and dopamine levels in the medial prefrontal cortex, nucleus accumbens (10), striatum (11), amygdala (12), and hypothalamus (13). The decrease in brain 5-HT and dopamine levels was accompanied by a reduced density of 5-HT neurons in the dorsal raphe nucleus and dopamine neurons in the substantia nigra (13).

With regards to the hippocampus, MIA decreased local 5-HT and dopamine levels (14), densities of serotonin-1A (5-HT_{1A}) and glucocorticoid receptors (10, 15), concentrations of the brain-derived neurotrophic factor (BDNF), and impaired adult neurogenesis in the hippocampus (16). To the authors' best knowledge, the effects of MIA on the excitability of hippocampal neurons in offspring have not yet been investigated. The knowledge of the excitability pattern of hippocampal neurons under normal and maternal stress–induced conditions is, however, important for understanding the mechanisms of hippocampal neuronal plasticity. The present study is, therefore, aiming to test the hypothesis that MIA leads to impaired functioning of hippocampal pyramidal neurons isolated from the hippocampi of newborn offspring. The novelty of the present study is that it is the first to assess the effect of the MIA on the excitability of the individual offspring hippocampal pyramidal neurons very early after birth.

Results

Prenatal LPS Does Not Alter V_{rest}

MIA by LPS did not affect V_{rest} of hippocampal neurons isolated from newborn offspring, as measured at the DIV4-13 of their cultivation. At DIV10, however, a statistically significant interaction between sex and prenatal LPS treatment was observed ($F_{1,63} = 10.40$, $p = 0.002$). Prenatal LPS tended to increase V_{rest} in females and decrease it in males; nevertheless, the Tukey post-hoc test did not reveal any between-group differences. At DIV13, statistically significant sex differences in V_{rest} were observed ($F_{1,29} = 9.06$, $p = 0.005$); it was higher in females compared to the males, regardless of prenatal LPS treatment (not shown).

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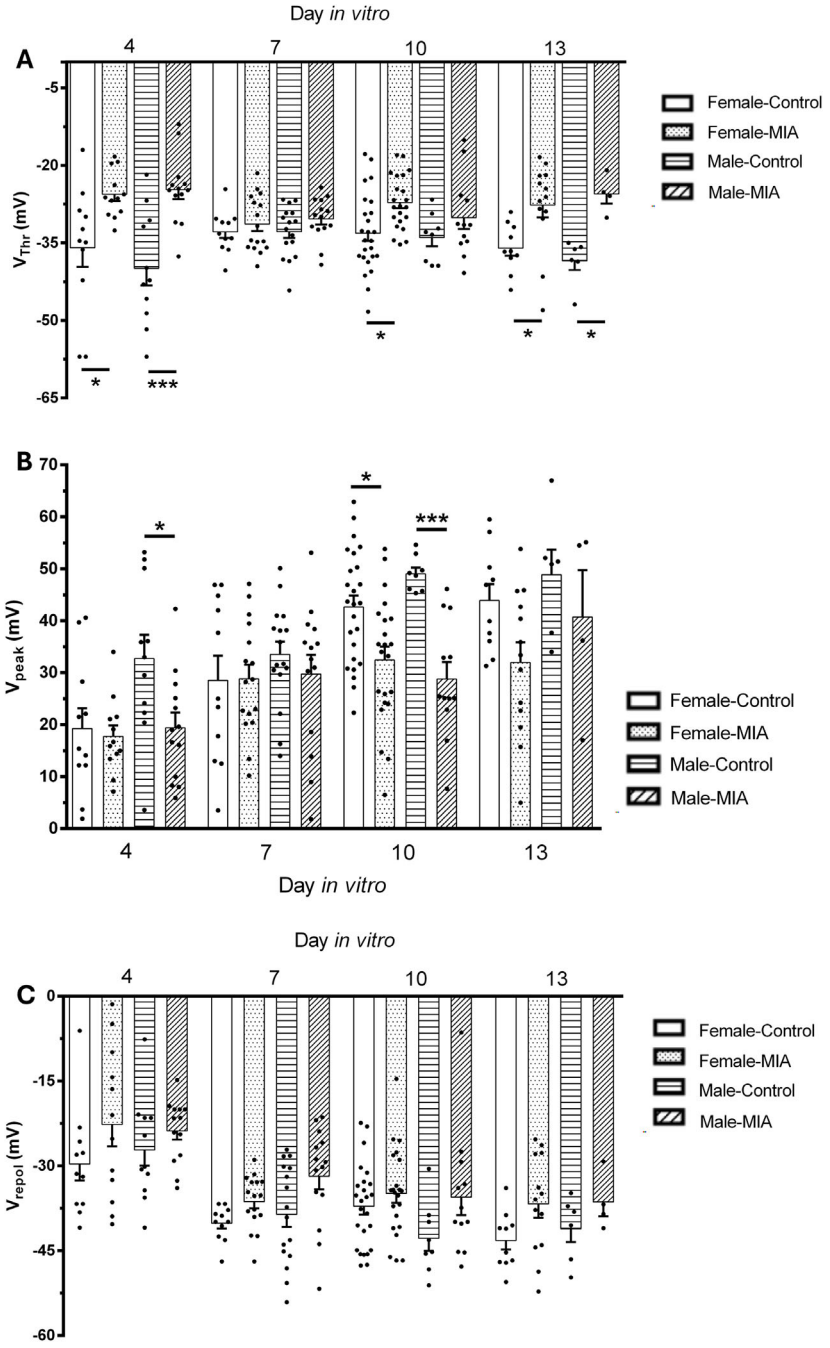

Figure 1. Effect of MIA on the membrane action potential threshold (B), peak (C), and repolarization (D) values potential of the offspring hippocampal neurons. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$ in comparison with controls, Tukey post-hoc test.

Prenatal LPS Increases V_{thr} and Vrep and Decreases Vpeak

Prenatal LPS had a statistically significant increasing effect on the V_{thr} as measured at DIV4 ($F_{1,43} = 23.64$, $p < 0.0001$), DIV10 ($F_{1,63} = 10.83$, $p = 0.007$), and DIV13 ($F_{1,29} = 18.41$, $p = 0.0002$; Figure 1A). Prenatal LPS had also a statistically significantly decreased V_{peak}, as measured at DIV4 ($F_{1,43} = 4.73$, $p = 0.04$) and DIV10 ($F_{1,63} = 29.96$, $p < 0.0001$, Figure 1B) and increased V_{rep}, as measured at DIV7 ($F_{1,53} = 7.87$, $p = 0.007$), DIV10 ($F_{1,63} = 4.67$, $p = 0.03$), and DIV13 ($F_{1,29} = 4.44$, $p = 0.04$, Figure 1C). At DIV4, V_{peak} in females was higher compared to the males ($F_{1,43} = 4.94$, $p = 0.03$). At DIV10, the V_{peak} difference between control and prenatally LPS-treated rats was higher in females compared to the males ($F_{1,43} = 4.21$, $p = 0.046$). No sex differences and no sex × treatment interaction for these parameters were observed. The values from the individual neurons/recordings are shown in the figure using the dots.

Prenatal LPS Increases T_{lat} and Decreases $V_{max\text{-}ascend}$ and $V_{max\text{-}descend}$

Prenatal LPS had a statistically significant increasing effect on the T_{lat}, as measured at DIV4 ($F_{1,43} = 234.70$, $p < 0.0001$) and DIV7 ($F_{1,53} = 42.54$, $p < 0.0001$; Figure 2A). Prenatal LPS statistically significantly suppressed the $V_{max\text{-}ascend}$, as measured at DIV4 ($F_{1,43} = 74.59$, $p < 0.0001$), DIV7 ($F_{1,53} = 47.23$, $p < 0.0001$), DIV10 ($F_{1,63} = 4.98$, $p = 0.03$), and DIV13 ($F_{1,29} = 9.93$, $p = 0.004$; Figure 2B), and $V_{max\text{-}descend}$, as measured at DIV4 ($F_{1,43} = 127.00$, $p < 0.0001$), DIV7 ($F_{1,53} = 46.31$, $p < 0.0001$), and DIV13 ($F_{1,29} = 6.99$, $p = 0.01$, Figure 2C). At DIV4, $V_{max\text{-}ascend}$ was higher in

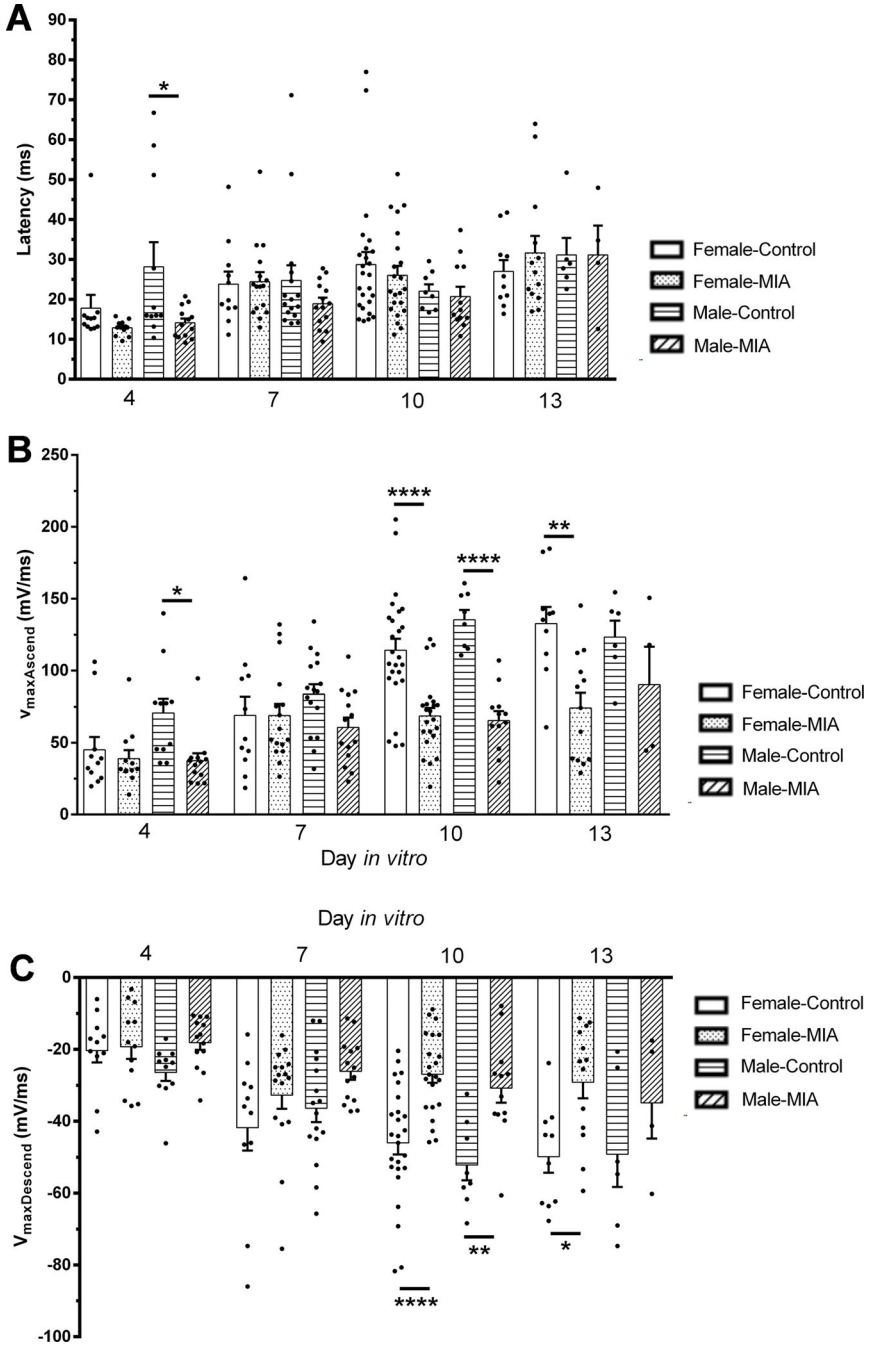

Figure 2. Effect of the MIA on the latency time (A) and ascend (B) and descend (C) velocities of the APs generated by the offspring hippocampal neurons. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$ in comparison with controls, Tukey post-hoc test. The numbers of recordings from individual neurons are shown on the bars.

females compared to males ($F_{1,43} = 4.11$, $p = 0.049$). No sex differences in the action potential (AP) threshold potential and latency time and no sex × treatment interaction for these parameters were observed. The values from the individual neurons/recordings are shown in the figure using the dots.

Prenatal LPS Suppressed the Depolarizing Current Pulse–induced and Spontaneous Activity of Hippocampal Neurons

Prenatal LPS significantly suppressed the number of APs within the depolarizing current pulse (DCP)-induced AP series, as measured at DIV10 ($F_{1,63} = 22.06$, $p < 0.0001$) and DIV13 ($F_{1,29} = 15.36$, $p = 0.005$; Figure 3A). No sex differences and no sex × treatment interactions were observed, as measured at DIV10-13. The spontaneous activity was significantly decreased as well, but only at DIV13 and only in male rats (Figure 3B). A significant effect of prenatal LPS treatment ($F_{1,19} = 5.60$, $p = 0.03$) and significant sex × treatment interaction ($F_{1,19} = 6.38$, $p = 0.02$) was detected. The values from the individual neurons/recordings are shown in the figure using the dots.

Discussion

The results of the present study show that maternal MIA induced significant alterations in the waveform of the APs generated by offspring hippocampal neurons. Thus, the APs generated by hippocampal neurons isolated from the offspring of LPS-treated dams are characterized by decreased threshold, peak, and repolarization potentials, decreased AP ascend and descend speeds, and increased latency time, compared to the

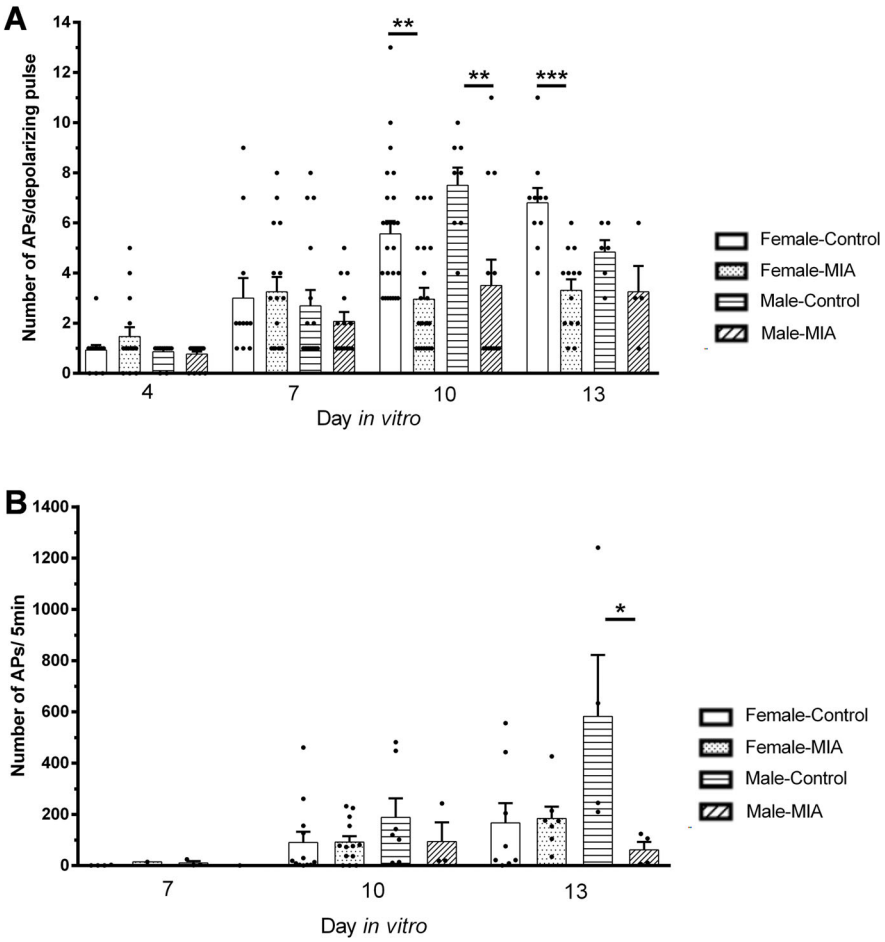

Figure 3. Effect of the MIA on the evoked (A) and spontaneous (B) activity of the offspring hippocampal neurons. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ in comparison with controls, Tukey post-hoc test. The numbers of recordings from individual neurons are shown on the bars.

APs generated by hippocampal neurons isolated from offspring of control dams. MIA also led to decreased DCP-induced and spontaneous activity of hippocampal neurons in offspring. The summary of the effects of prenatal LPS on the excitability of hippocampal neurons is shown in Table 1.

We found that the MIA did not alter the resting membrane potential of neurons isolated from the hippocampi of newborn offspring, as measured during the early (DIV3-7) and late (DIV10-13) stages of *in vitro* maturation. In our previous study (17), however, we reported that maternal stress led to an enhancement of V_{rest} of the neurons isolated from the hippocampi of newborn offspring, as measured at DIV4-10. The difference between the results of the present and previous studies might be explained by the nature of the stress situation and the time of its application. Our previous study examined the effect of pregestational chronic unpredictable stress. The present study studied the effect of stress associated with MIA during the third trimester of gestation.

It was found that MIA led to the increased threshold potential of AP generation in the offspring hippocampal neurons. As a result, the AP latency time was increased, and the number of APs observed during the DCP application decreased. Other intrinsic AP characteristics affected by the MIA decreased ascend and descend speeds and increased repolarization potentials. Therefore, maternal stress likely alters the voltage-dependent ion channels' expression and/or activity in the AP generation. Indeed, stress-induced changes in the expression of certain voltage-dependent ion channels, such as Kv1 (18) and Kv7 (19) voltage-dependent potassium channels, were reported. The exact mechanism mediating the effect of maternal stress on the expression and/or activity of the voltage-dependent ion channels in the offspring neurons is not yet known. However, it is likely to be based on the interactions between maternal and embryonal stress hormones (e.g., corticosteroids), pro- (e.g., interleukins-1 and 12: IL-1/12, tumor necrosis factor-alpha: TNF-α, and interferon-gamma: IFNγ) and anti-inflammatory (e.g., interleukins-4, 6 and 10: IL-4/6/10), cytokines, and neurotrophic factors (e.g., brain-derived neurotrophic factor: BDNF) (20–22).

Table 1. Summary of the statistically significant effects of the MIA on the excitability of glutamate neuron isolates from the offspring hippocampi

	DIV4	DIV7	DIV10	DIV13
Resting potential	0	0	0[1]	0[2]
AP threshold potential	↑	0	↑	↑
AP latency time	↑	↑	0	↑
AP maximum ascend speed	↓[2]	↓	↓	↓
AP maximum descent speed	↓	↓	0	↓
AP peak potential	↓[2]	0	↓[1]	0
AP repolarization potential	0	↑	↑	↑
Evoked activity	0	0	↓	↓
Spontaneous activity	n/e	0	0	↓[1]

AP, action potential; DIV, day-in-vitro; 0, np effect; ↑, increasing effect; ↓, decreasing effect; n/e, not evaluated; [1], significant interaction between sex and prenatal LPS treatment; [2], significant sex difference.

Another interesting finding of the present study is that prenatal LPS decreased the average peak value of the APs generated by hippocampal neurons isolated from the newborn offspring. This finding is similar to that of a previous study (23). However, Grigoryan and Segal found that prenatal stress tended to decrease the V_{peak} potential of APs generated by offspring hippocampal neurons, but the effect was not statistically significant. In the present study, the effect of the MIA was significant. These differences might be explained by the nature of the stressors being applied: forced swimming and cage declination in Grigoryan and Segal's *versus* MIA in this study.

We found that MIA decreased the depolarization pulse–induced and spontaneous generation of the APs in the pyramidal neurons isolated from newborn male hippocampi. The firing activity of the neurons is the most fundamental characteristic determining the neurotransmitter release from the nerve terminals (24). It is, therefore, likely that the MIA led to decreased glutamate neurotransmission in the offspring hippocampi and perhaps in other brain areas as well.

As explained in our previous studies, the depolarization pulse–induced firing activity of the cultivated hippocampal neurons results from the direct activation of the voltage-dependent sodium channels. It is, therefore, primarily dependent on the intrinsic properties of the neurons. The spontaneous activity, however, depends on external excitatory synaptic inputs. It is consequently determined by the whole neuronal network (17, 25). MIA-induced decrease in the evoked activity of the hippocampal neurons isolated from the neonatal offspring brain might thus result from the increased AP threshold potential, which may, in turn, be caused by the abnormal expression of some voltage-dependent ion, for example, potassium channels (18, 19).

As in our previous studies (17, 25), spontaneous activity of the cultivated hippocampal neurons could be detected during the late stages of the cultivation (DIV10-13), when interneuronal synaptic connections are developed. Thus, the MIA-induced changes in the spontaneous activity of hippocampal neurons may be due to abnormal neuronal network development. It has been reported that stress may alter the hippocampal network development, for example, it may reduce the number of synaptic connections between the neurons *via* a mechanism involving various neurotrophic factors, such as BDNF (26, 27). Even though the actual networks were formed in *in vitro* conditions, which were similar for both groups, the previous exposure of the neurons or their precursors to the stress hormone and/or inflammatory cytokines putatively affected their future ability to create the networks.

Excitatory glutamatergic and inhibitory GABAergic synaptic inputs mediate the spontaneous activity of cultivated hippocampal neurons (28). Prenatal stress likely decreased the strength of the excitatory and/or increased the strength of the inhibitory synaptic inputs of the offspring hippocampal neurons. It has indeed been reported that prenatal stress increased the frequency of the miniature inhibitory postsynaptic currents recorded in the offspring hippocampal neurons (23).

While our present study reported that MIA suppressed the spontaneous activity of the offspring hippocampal neurons, a stimulatory effect of maternal stress exposure on the cultivated neurons isolated from the offspring hippocampi was observed in our previous experiments (17). As stated above, the difference between the present and previous studies' results might be explained by the stressor's nature and the time of its application.

Hippocampal glutamate circuits are fundamental in memory consolidation, retrieval, and cognitive performance (29). They also have a critical role in anxiety and depressive-like behavior (30). Decreased excitability of the hippocampal glutamate neurons, observed in this study, may explain, at least in part, decreased cognitive performance (12) and increased anxiety (31) and depressive-like behavior (16) in the offspring of the MIA dams reported in previous studies. It is known that children of women suffering from an infectious disease during pregnancy have a higher risk of future development of depression (1), schizophrenia (2–6), and autism (7). The results of the present study suggest that the early postnatal suppression of the excitability of hippocampal neurons might underline these epidemiological observations. Early-life therapeutic interventions, stimulating neurotransmission within the hippocampal area, applied using noninvasive, low-risk techniques such as transcranial magnetic stimulation (32), may, therefore, reduce the risk of future-life psychopathologies in the children of women who experienced infectious disease during the pregnancy. However, the risks and benefits of these interventions must be very carefully assessed. Animal models can be used in these assessments; however, the limitation of these models, which results from the difference between rodents and human brains, must be considered. Speaking specifically about the LPS-based model of the MIA, its major limitation is the fact that it primarily models bacterial infection. At the same time, from the epidemiological point of view, higher risk might be expected from viral infections.

In conclusion, our study's results, together with the results of previous studies from our (17) and other (23) groups, indicate that maternal stress induces significant alterations in the excitability pattern of the offspring hippocampal neurons. The nature of the maternal stress–induced alterations depends on the type of stressors applied (e.g., physical stressors versus immune activation) and the time of the application (e.g., pregestational versus prenatal). Interactions between maternal and embryonal stress hormones, cytokines, neurotrophic factors, embryonal ligand-(glutamate and GABA), and voltage-dependent ion channels might underline the nature of the maternal stress–induced alterations of the excitability of the offspring hippocampal neuronal circuits.

Materials and Methods

Animals

Adult female (200–250 g) and male (250–300 g) Wistar rats were ordered from the Animal Breeding facility of the Institute of Experimental Pharmacology and Toxicology, Centre for Experimental Medicine, Slovak Academy of Sciences (Dobra Voda, Slovakia). Animals were housed under standard laboratory conditions (temperature: 22 $\pm$ 2°C, humidity: 55% $\pm$ 10%) with a 12-h light/12-h dark cycle (lights on at 7 a.m.). Pelleted food and tap water were available ad libitum. All experimental procedures were approved by the Animal Health and Animal Welfare Division of the State Veterinary and Food Administration of the Slovak Republic (Permit number Ro 3592/15-221) and complied with the Directive 2010/63/EU of the European Parliament and of the Council on the Protection of Animals Used for Scientific Purposes.

MIA

After an acclimatization period of 1 week, the animals were placed in cages with one male and three females in each. Vaginal smears were taken daily between 7 and 8 a.m. and examined under light microscope. The day sperm cells were detected was considered as day 0 of gestation. During days 15–19 of the gestation, LPS-treated dams were once per day subcutaneously injected with LPS at increasing doses of 20, 20, 40, 40, and 80 μg/kg, as described previously (8, 12). The third trimester of gestation was chosen for the LPS administration because it is a critical developmental period for specific central nervous system (CNS) structures (33). Control dams were injected with saline. On day 20 of gestation, dams were placed in individual cages. The birth usually occurs on day 21 of gestation.

Primary Culture of Hippocampal Neurons

As previously described, hippocampal neurons were isolated from newborn Wistar rats of both sexes at the first postnatal day (25, 34). Hippocampi were removed and transferred to ice-cold isolation solution containing (in mM): 137 NaCl; 5.4 KCl; 1.1 $Na_2HPO_4 \times 2H_2O$; 1.1 KH_2PO_4; 6.1 Glucose and 1 Kynurenic acid; pH 7.3 with NaOH. Tissue was chopped and incubated in a predigestion solution (Leibovitz L-15 Medium; 25 U/mL Papain; 2 mM Kynurenic acid) for 25 to 30 min at 37°C in an atmosphere containing 5% CO_2. Digested tissue was washed with cold STOP solution (isolation solution mixed with a heat-inactivated fetal bovine serum in a ratio of 3:1). Finally, hippocampi were transferred into incubation media containing high glucose (4.5 g/L) Dulbecco's Modified Eagle's (DMEM) Medium supplemented with 10% heat-inactivated fetal bovine serum, antibiotics (75,000 IU/L penicillin and 75 mg/L streptomycin), 2 mM $MgCl_2$, 10 nM progesterone, 100 μM putrescine, and 12.5 mg/mL ITSS (25 mg insulin, 25 mg transferrin, and 25 μg Na-selenite). In incubation media, hippocampi were consecutively triturated with three glass Pasteur

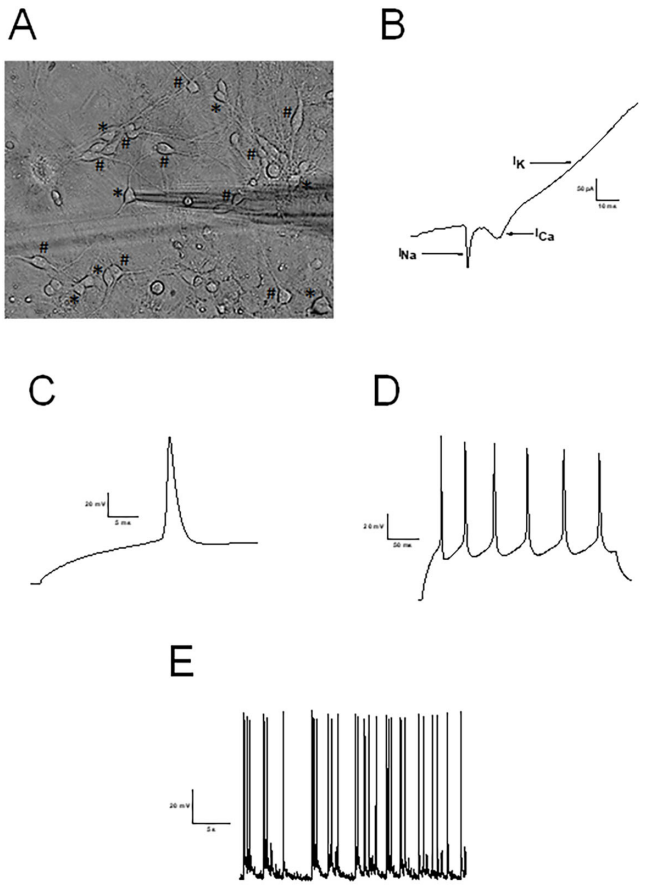

Figure 4. Identification of glutamate pyramidal neurons in primary cultures prepared from neonatal rat hippocampi and their evoked and spontaneous activity. (A) Characteristic morphology of pyramidal (*) and nonpyramidal (#) neurons. (B) Sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+) currents, characteristic for hippocampal pyramidal neurons, recorded immediately after the opening of the neurons, under the whole-cell voltage-clamp using voltage ramp from −80 to +80 mV with a speed of 1.6 mV/1 ms and holding potential of −70 mV. (C) Single AP generated by a DCP of 30 pA in DIV7 cultivated neurons. (D) AP series generated by a DCP of −10 pA in DIV10 cultivated neuron. (E) Spontaneous AP generated by a neuron in DIV13 culture.

pipettes with decreasing diameters. From the final single-cell suspension, hippocampal neurons were seeded at a density of 5×10^4 cells/cm^2 on 35 mm plastic Petri dishes containing glass coverslips (Sarstedt, Slovakia) coated with poly-D-lysine (50 μg/1 mL/1 cm^2) in incubation media containing penicillin/streptomycin. After 24 h, the medium was exchanged for an antibiotics-free medium. At days 4 to 5 *in vitro* (DIV4-5) Cytosine β-D-arabinofuranoside (1 μM) was added to reduce the proliferation of nonneuronal cells. Neurons were incubated in a humidified incubator in an atmosphere containing 5% CO_2 at 37°C up to DIV14. Unless mentioned otherwise, all chemicals were purchased from Sigma Aldrich, Slovakia.

Electrophysiological Recordings

Recordings were done in the whole-cell patch-clamp configuration at room temperature using a HEKA EPC10 amplifier (HEKA Electronics, Lambrecht, Germany). Patch pipettes with resistance ranging from 4 to 5 MΩ were fabricated from borosilicate glass capillaries (Sutter Instruments, Novato, CA). Pyramidal neurons were identified by their characteristic physical appearance (triangular soma; Figure 4A) and the presence of potassium ($I_{K)}$, sodium (I_{Na}), and calcium (I_{Ca}) currents, measured immediately after the opening of the cell (Figure 4B). As previously described, AP firing was measured under the current clamp conditions (25, 34). The intracellular solution contained (in mM): 120 K-gluconate; 20 KCl; 2 $MgCl_2$; 2 Na_2ATP; 0.25 Na_2GTP; 10 HEPES; pH 7.3 (with KOH). The osmolarity of an intracellular solution was approximately 290–300 mOsmol/L in all cases (measured by Osmomat 030-Gonotec, Germany). The osmolarity of an extracellular solution was set to a value of 2–3 mOsm/L lower than the osmolarity of the corresponding intracellular solution. DCP can activate a single AP (Figure 4C) or AP series (Figure 4D) in cultured hippocampal neurons after DIV4-5. We have used this protocol on the days DIV8-9, when the expression of voltage-dependent I_{Na}, I_K, and I_{Ca} is developed. In these experiments, resting membrane potential was maintained at −70 mV. Evoked AP series were activated by a series of six 300-ms-long DCPs with amplitudes increasing with a step of +50 pA. Longer maturation was necessary for the development of spontaneous activity. After DIV10-12, hippocampal neurons in a primary culture become spontaneously active (Figure 4E). The experiments were done on DIV13-14 when about 80% of all tested cells were spontaneously active. Spontaneous activity was recorded for 5 min at an intrinsic membrane potential of each cell. The mean membrane potential corrected for a liquid junction potential was -65.2 ± 0.4 mV.

Data and Statistical Analysis

The following characteristics of the AP waveform and neuronal excitability were analyzed: membrane resting potential (V_{rest}), AP latency time (t_{lat}) and threshold (V_{thr}), peak (V_{peak}), and repolarization (V_{rep}) potentials, and maximal ascend ($V_{max\text{-}ascend}$) and descent ($V_{max\text{-}descend}$) velocities. V_{thr} was detected as an electrical potential value at the time point where its second derivation by time reaches the local maximum. The t_{lat} was measured as the time between the start of the DCP and the detection of V_{thr}, as described previously. $V_{max\text{-}ascend}$ and descent $V_{max\text{-}descend}$ were detected as the local minimum and maximum of the derivative of membrane electrical potential by time, respectively, as described previously (35). The effects of sex, prenatal LPS treatment, and sex × treatment interaction differences for each parameter were assessed using the two-way analysis of variance (ANOVA), followed by the Tukey post-hoc test. Before the analysis by ANOVA, data normality and homoscedasticity were verified using Shapiro–Wilk's and Levene's tests, respectively. The probability of $p < 0.05$ was considered as significant.

Data Availability Statement

The original research data are available upon request.

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Authors Contribution

E.D., L.M., D.J., and L.L. planned the study and formulated the working hypothesis. L.M., R.M., and K.C. conducted experiments. L.M., R.M., and E.D. analyzed the results. L.M., L.L., and E.D. wrote the manuscript. All authors critically proofread the manuscript and approved it for publication.

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Authors Disclosures

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Brain Medicine

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RESEARCH REPORT

Manic symptoms in schizophrenia spectrum disorders

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This study investigated the presence of manic symptoms in stable patients diagnosed with schizophrenia spectrum disorders (SSDs) aiming to identify their association with clinical symptoms. A total of 75 out-patients, 41.3% female [47.81 (±10.521) year-old] were assessed using the Young Mania Rating Scale (YMRS), Positive and Negative Syndrome Scale (PANSS), Generalized Anxiety Disorder-7 scale (GAD-7), and Risk Assessment of Suicidality Scale (RASS). Participants were divided into two groups based on YMRS scores: Group 1, without or with minimal symptoms of mania (YMRS ≤ 10) and Group 2, with distinct manic symptoms (YMRS > 10). We performed statistical analysis using the IBM SPSS version 29.0. Our analysis revealed a positive significant correlation between YMRS total score and PANSS total score ($r^2 = 0.516$, $p = 2.15 \times 10^{-6}$), PANSS-Positive subscore ($r^2 = 0.600$, $p = 1.31 \times 10^{-8}$) and PANSS-General Psychopathology subscore ($r^2 = 0.444$, $p = 6.646 \times 10^{-5}$), Bonferroni corrected at $p = 0.0004$. Moreover, positive symptoms as assessed by the PANSS-Positive subscale score differed significantly between the two YMRS groups [$t(73) = 3.982$, $p = 0.00016$, $d = 1.040$]. Linear regression analysis showed that the severity of positive symptoms predicted the occurrence of manic symptoms. This study could serve as a pilot study, observing manic symptoms in SSDs and as recruitment goes on, it is expected to yield more robust evidence of their prevalence in SSDs and their associations with clinical symptoms forming the phenotypic characterization basis for further dimensional research in the psychopathology and etiopathogenesis of SSDs.

Keywords: Global functionality, mania, manic symptoms, neurocognitive functions, PANSS, schizophrenia spectrum disorders, suicidality, YMRS.

Introduction

Schizophrenia is a severe mental disorder characterized by significant alterations in thought, perception, emotion, and behavior. Often regarded as a single mental disorder, it appears to reflect considerable heterogeneity. Schizophrenia symptoms are typically grouped into positive, negative, and disorganized symptoms, but no single symptom cluster is pathognomonic of schizophrenia (1). While mania is generally easy to recognize (2), severe cases with psychotic features can be misdiagnosed as schizophrenia, and milder cases may be mistaken for personality disorders (3). Furthermore, it is critical to distinguish between mania and manic symptoms. Whereas a manic episode significantly impacts various domains of functioning, may include psychotic symptoms, and usually requires hospitalization (4), manic symptoms do not necessarily meet the criteria for a full-blown manic episode.

Manic symptoms can appear within a range of psychiatric diagnoses, and do not exclusively form part of manic episodes. The relationship between schizophrenia and manic symptoms remains an area of limited research. Evidence, however, indicates the presence of manic symptoms across various diagnostic categories, including schizophrenia and schizoaffective disorder (5). Moreover, van Os and Kapur (2009) proposed changing the categorical dichotomy of schizophrenia and bipolar disorder (BD) to a dimensional conceptualization (6). Diagnosis of schizoaffective disorder requires meeting criteria for a major mood episode for most of the lifetime of the illness as well as psychotic symptoms without overt mood symptoms within a 2-week period (7). Manic symptoms are often part of schizoaffective disorder, but no consensus currently exists as to whether this disorder lies within the schizophrenia spectrum disorders (SSDs), the mood disorders or both (8–11).

Manic symptoms can significantly impact the clinical course and prognosis of schizophrenia (12) and as such, their assessment has been included in the mania domain of the Clinical-Rated Dimensions of Psychosis Symptom Severity (CRDPSS) scale proposed by DSM-5 for assessing the severity of psychotic symptoms in schizophrenia (13). A Korean study examining the psychometric properties of the Young Mania Rating Scale (YMRS) in SSDs, using a receiver operating characteristic analysis, found the optimal cut-off score for distinguishing schizophrenia patients with manic symptoms from those without to be 10, with a sensitivity of 88.3% and a specificity of 75.6% (14). This is in contrast to the cut-off point of 12 taken to be the threshold for diagnosing mania in mood disorders (15). They concluded that a YMRS score of 10 indicates mild mania severity on the Clinical Global Impression (CGI) scale, making it a reasonable threshold for identifying manic symptoms in patients with SSD.

Overlooking mania could result in missed opportunities to use pharmacological treatments and may lead clinicians to make excessively pessimistic prognoses (16). Individuals with schizophrenia often experience a more severe course of illness and have worse prognoses than those with schizoaffective disorder. Further research is necessary to categorize better the various clinical phenomena that fall under the umbrella of manic syndromes and SSDs. This study aims to investigate the presence of mania in stable patients diagnosed with SSDs. We hypothesized that in patients with SSD, manic symptoms are associated with clinical psychopathology.

Results

A total of 75, 44 male (58.7%) patients with SSD [mean age 43.55 (±11.800) years] and 31 female (41.3%) patients with SSD [mean age 47.81 (±10.521) years] met the inclusion criteria. The mean YMRS score for the total sample was 6.36 (±5.753). We dichotomized our group according to the severity of YMRS scoring and used the YMRS cut-off score of 10, suggested to be appropriate for the detection of mania in SSDs (Kim *et al*., 2018). The total sample was dichotomized into two groups: Group 1, without or with minimal symptoms of mania (YMRS ≤ 10) and Group 2, with distinct manic symptoms (YMRS ≥ 10). Group 1 ($N = 55$) had a mean YMRS total score of 3.42 (±3.004) and Group 2 ($N = 20$) had a mean YMRS total score of 14.45 (±3.052). The two groups differed significantly in terms of total mean YMRS scoring [$M = 11.032$ [95% confidence interval (CI): 9.462 to 12.602], t (73) = 14.005, $p = 2.252 \times 10^{-22}$, $d = 3.657$], as expected. As Levene's test for equality of variances was non-significant ($p = 0.807$), we could safely assume that the data were normally distributed. A *post-hoc* power calculation for independent t-tests at $\alpha = 0.05$ found the statistical power to be equal to 1.000.

Descriptive statistics were used to provide a comprehensive summary of the mean YMRS individual item and total score for the total sample (Table 1). Table 2 summarizes the demographic characteristics of the participants without or with minimal manic symptoms and mania. Sex distribution and family history of mental illness did not differ significantly between the two groups (*Fisher's exact test* = 0.147 and *Fisher's exact*

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Table 1. YMRS total score and YMRS individual items' mean (SD) scores and 95% CI of the means for $N = 75$ patients with SSD

YMRS Items	Min	Max	Mean ($N = 75$)	95% CI of Mean		Standard Deviation (SD)
				Upper	Lower	
1. Elevated Mood	0	3	0.56	0.39	0.73	0.758
2. Increased Motor Activity/Energy	0	3	0.31	0.16	0.45	0.636
3. Sexual Interest	0	2	0.12	0.02	0.22	0.434
4. Sleep	0	3	0.20	0.05	0.35	0.637
5. Irritability	0	4	0.61	0.39	0.84	0.971
6. Speech (Rate and Amount)	0	6	0.89	0.55	1.24	1.512
7. Language/Thought Disorder	0	3	0.64	0.46	0.82	0.765
8. Thought Content	0	8	1.03	0.65	1.41	1.652
9. Disruptive/Aggressive Behavior	0	3	0.37	0.22	0.52	0.653
10. Appearance	0	4	0.67	0.46	0.87	0.890
11. Insight	0	4	0.96	0.63	1.29	1.418
Total YMRS Score	**0**	**22**	**6.36**	**5.04**	**7.68**	**5.753**

Table 2. Demographics of the total sample ($N = 75$) dichotomized according to YMRS score

YMRS Total Score [*N*, Mean (SD)]	Group 1 (≤10)	Group 2 (>10)
Age (years)	45.35 (11.409), $N = 55$	45.20 (11.719), $N = 20$
Body Mass Index (BMI, kg/m^2)	27.55 (4.879), $N = 50$	26.29 (7.459), $N = 17$
Antipsychotic Dose (in Olanzapine Equivalents, mg)	19.96 (17.416), $N = 48$	22.17 (18.183), $N = 18$
Antidepressant Dose (in Fluoxetine Equivalents, mg)	43.10 (37.24), $N = 19$	33.03 (18.86), $N = 7$
Benzodiazepine Dose (in Diazepam Equivalents, mg)	15.51 (8.434), $N = 10$	20.00 (7.071), $N = 4$
Total Number of Episodes	2.41 (1.643), $N = 54$	1.95 (1.268), $N = 19$
Total Number of Hospitalizations	1.20 (1.592), $N = 55$	0.90 (1.483), $N = 20$
Age (years) at First Episode Psychosis	28.40 (10.399), $N = 55$	27.70 (10.854), $N = 20$
Total Number of Suicidal Attempts	1.85 (2.430), $N = 55$	1.75 (2.291), $N = 20$
Total Illness Duration (years)	17.15 (12.002), $N = 55$	17.50 (11.199), $N = 20$
Sex (*N*, %)		
Male	35 (63.6)	9 (45.0)
Female	20 (36.4)	11 (55.0)
Marital Status (*N*, %)		
Single	35 (66.0)	12 (60.0)
Married	9 (17.0)	5 (25.0)
Separated	1 (1.9)	0 (0.0)
Divorced	6 (11.3)	1 (5.0)
Lives with Other	1 (1.9)	1 (5.0)
Widow/Widower	1 (1.9)	1 (5.0)
Employment (*N*, %)		
Used to Work, but Now Unemployed	35 (64.8)	9 (45.0)
Never Worked, Nor Working Now	6 (11.1)	4 (20.0)
Employee (Private or Public Sector)	6 (11.1)	3 (15.0)
Freelancer (Salesman/Skilled Worker)	1 (1.9)	0 (0.0)
Doctor/Lawyer/Engineer/Priest/Teacher	3 (5.6)	1 (5.0)
University Student	1 (1.9)	1 (5.0)
Manual Worker/Builder/Farmer/Etc.	2 (3.7)	2 (10.0)
Family History of Mental Illness		
no	20 (36.4)	7 (35.0)
yes	35 (63.6)	13 (65.0)
Drug Use in the Past		
no	33 (60.0)	12 (63.2)
mild	15 (27.3)	3 (15.8)
severe	7 (12.7)	4 (21.1)
Drug Use at Present		
no	52 (94.5)	16 (84.2)
mild	3 (5.5)	2 (10.5)
severe	0 (0.0)	1 (5.3)

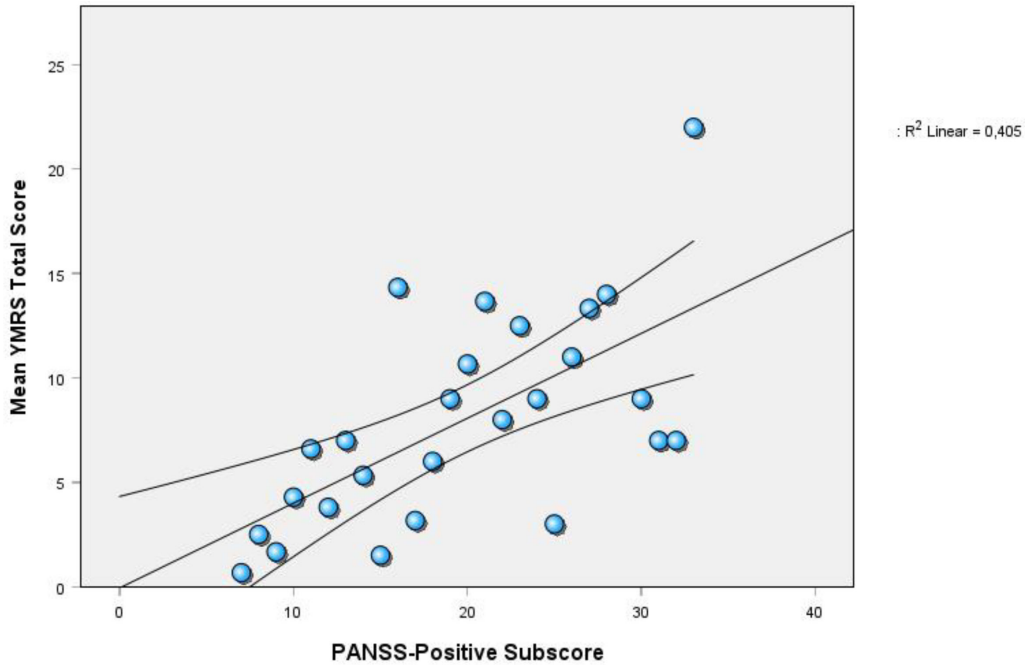

Figure 1. Simple scatter plot of PANSS-Positive subscore versus mean YMRS total score.

test = 1.000, respectively). For both, a *post-hoc* power calculation for chi-square tests with $df = 1$ at $\alpha = 0.05$ and for a medium effect size of 0.33, found the statistical power to be equal to 0.820.

Interestingly, we found a positive significant correlation between YMRS total score and the Positive and Negative Syndrome Scale (PANSS) total score ($r^2 = 0.516$, $p = 2.147 \times 10^{-6}$), the PANSS-Positive subscore ($r^2 = 0.600$, $p = 1.310 \times 10^{-8}$; Figure 1), and the PANSS-General Psychopathology subscore ($r^2 = 0.444$, $p = 6.646 \times 10^{-5}$), but the correlation between YMRS total score and PANSS-Negative subscore failed to reach significance (Table 3). Furthermore, independent-samples *t*-tests were performed to explore mean differences in PANSS total and subtest, Generalized Anxiety Disorder -7 scale (GAD-7), and Risk Assessment of Suicidality Scale (RASS) scores between participants without or with minimal symptoms of mania, and in those with manic symptoms. Positive symptoms scoring, as assessed by the PANSS-Positive subscale, was the only psychopathology measure that stood the stringent criterion of the Bonferroni multiple correction and showed a statistically significant difference between the two YMRS groups [PANSS-Positive subscore *mean diff* = 6.841 (95% CI: 3.417to 10.265), $t(73) = 3.982$, $p = 0.00016$, $d = 1.040$] (Table 4). A *post-hoc* power calculation based on data from this independent *t*-test comparison, for $d = 1.040$ and $\alpha = 0.05$, found the statistical power to be over 0.999, a more than adequate value for detecting an effect. More specifically, analyzing correlations between individual YMRS items and the PANSS total and subscale scores (Table 5), PANSS-Positive subscore was positively correlated with YMRS item 7 on language and thought disorder ($r^2 = 0.449$, $p = 5.239 \times 10^{-5}$) and YMRS item 11 on insight ($r^2 = 0.522$, $p = 1.593 \times 10^{-6}$) at a *post-hoc* calculated power of 0.990 and 0.999, respectively, given $\alpha = 0.05$.

Finally, linear regression established that the PANSS-Positive subscale score could significantly predict the YMRS total score [$F(1,73) = 36.851$, $p = 5.214 \times 10^{-8}$]. The YMRS total score accounted for 32.6% of the explained variability in PANSS-Positive score.

Discussion

In this study, we found an increased number of manic symptoms denoting the presence of mania in just over one in four (26.7%) stable participants with SSDs. An earlier epidemiological study from Canada found that the prevalence of an episode of mania in patients with schizophrenia in the community was 17.7 % (17), and a more recent study showed significant subthreshold manic symptoms (YMRS score > 7) to be present in 25.1% of patients (18).

In this group of patients with SSD, we showed that positive symptoms were associated with mania. Interestingly, the severity of positive symptoms was found to predict the presence of manic symptoms, such that, the higher the PANSS-Positive score, the more likely the presence of manic symptoms. Our findings replicate results from a previous study on

Table 3. Spearman (r^2) correlation matrix for YMRS Total score versus PANSS total score and subscores with exact *p* values

	1	2	3	4
1. YMRS Total Score				
2. PANSS-Positive Subscore	0.600 $p = 1.310 \times 10^{-8}$			
3. PANSS-Negative Subscore	0.310 $p = 0.007$	0.463 $p = 2.829 \times 10^{-5}$		
4. PANSS-General Subscore	0.444 $p = 6.646 \times 10^{-5}$	0.783 $p = 1.079 \times 10^{-16}$	0.695 $p = 4.498 \times 10^{-12}$	
5. PANSS Total Score	0.516 $p = 2.147 \times 10^{-6}$	0.851 $p = 4.241 \times 10^{-22}$	0.805 $p = 3.023 \times 10^{-18}$	0.952 $p = 3.822 \times 10^{-39}$

Table 4. Comparison of total scores and subscores for PANSS, GAD-7, and RASS scales between the two groups according to YMRS scoring

YMRS Total Score ($N = 75$)	Group 1 (YMRS ≤10), $N = 55$	Group 2 (YMRS >10), $N = 20$
PANSS-Positive Subscore, Mean (SD)	*mean diff* = 6.841 (95% CI: 3.417 to 10.265), $t(73) = 3.982$, $p = 0.00016$, $d = 1.040$	
	14.25 (6.743)	20.95 (6.452)
PANSS-Negative Subscore, Mean (SD)	*mean diff* = 2.282 (95% CI: −1.690 to 6.254), $t(73) = 1.145$, $p = 0.256$, $d = 0.299$	
	18.86 (8.000)	21.10 (6.851)
PANSS-General Subscore, Mean (SD)	*mean diff* = 6.777 (95% CI: 1.197 to 12.358), $t(73) = 2.420$, $p = 0.018$, $d = 0.632$	
	33.98 (11.270)	40.65 (9.494)
PANSS Total Score, Mean (SD)	*mean diff* = 15.900 (95% CI: 4.672 to 27.128), $t(73) = 2.822$, $p = 0.006$, $d = 0.737$	
	67.10 (22.794)	82.70 (18.991)
GAD-7 Total Score	*mean diff* = 4.430 (95% CI: 0.455 to 8.404), *Mann-Whitney U* = 370.50, $Z = -2.07$, $p = 0.038$	
[Median (IQR), min-max and Mean (SD)]	4.00 (1–8), min 0 – max 27	9.80 (7.978)
RASS Total Score, Mean (SD)	*mean diff* = 50.750 (95% CI: −104.762 to 206.262), $t(73) = 0.651$, $p = 0.517$, $d = 0.172$	
	320.00 (284.617)	370.75 (22.267)

CI: Confidence Intervals, GAD – 7: Generalized Anxiety Disorder Assessment −7, IQR: Interquartile Range, M: mean, max: maximum, min: minimum, PANSS: Positive and Negative Syndrome Scale, RASS: Risk Assessment Suicidality Scale, YMRS: Young Mania Rating Scale.

175 patients with schizophrenia aiming to search for patterns in clinical symptomatology suggestive of the presence of mood disorders under the label of schizophrenia, also showing that mood symptoms correlate with positive symptoms (18).

Furthermore, to ascertain whether metabolic variability is associated with the clinical features of schizophrenia, Malaspina *et al*. (2021) examined the association of *N*-acetylaspartate (NAA) and choline (Cho) levels with clinical symptoms in patients with schizophrenia. They found a positive correlation between manic symptoms, as assessed by the YMRS, and whole-hippocampus multivoxel average choline millimolar concentration of Cho, denoting that both manic symptoms and positive symptoms reflect demyelination. On the contrary, negative symptoms were correlated with decreased NAA hippocampal levels reflecting a different pathophysiologic process, consistent with microgliosis/astrogliosis and/or lower vitality (19).

Table 5. Spearman's (r^2) correlation matrix for PANSS-Positive subscore versus individual YMRS item scores with exact *p* values

	1	2	3	4	5	6	7	8	9	10	11
1. PANSS-Positive Subscore											
2. Elevated Mood [YMRS1]	–										
3. Increased Motor Activity [YMRS2]	–	0.545 $p = 4.305 \times 10^{-7}$									
4. Sexual Interest [YMRS3]	–	–	–								
5. Sleep [YMRS4]	–	–	–	–							
6. Irritability [YMRS5]	–	–	–	–	–						
7. Speech [YMRS6]	–	0.473 $p = 1.812 \times 10^{-5}$	–	–	–	–					
8. Language/ Thought Disorder [YMRS7]	0.449 $p = 5.239 \times 10^{-5}$	0.444 $p = 6.614 \times 10^{-5}$	0.516 $p = 2.105 \times 10^{-6}$	–	–	0.468 $p = 2.258 \times 10^{-5}$	0.515 $p = 2.258 \times 10^{-6}$				
9. Thought Content [YMRS8]	–	–	–	–	–	–	–	0.685 $p = 1.196 \times 10^{-11}$			
10. Disruptive/ Aggressive Behavior [YMRS9]	–	–	–	–	–	0.446 $p = 6.185 \times 10^{-5}$	–	0.434 $p = 9.822 \times 10^{-5}$	–		
11. Appearance [YMRS10]	–	–	–	–	–	–	–	–	–	–	
12. Insight [YMRS11]	0.522 $p = 1.593 \times 10^{-6}$	–	–	–	–	–	–	–	–	–	–

Significant progress has been made in understanding the genetics of schizophrenia over the last 15 years, shedding light on the close relationship between SSDs and other conditions, particularly BD and childhood neurodevelopmental disorders. A clearer picture is emerging, suggesting that clinical heterogeneity partly reflects etiological heterogeneity. For example, several etiological pathways are influenced by the catechol-O-methyltransferase gene (*COMT*), including prefrontal cognition or emotional processing in the amygdala and the prefrontal cortex, in addition to other insults to the brain such as adolescent cannabis use. This means that the individual clinical phenotype may result from a combination of distinct symptom dimensions and their associated genetic risk factors (20).

COMT is an enzyme catalyzing the breakdown of dopamine and norepinephrine, thought to be involved in the pathophysiology of BD and schizophrenia. COMT striatal activity, but not the rs4680 (*COMT Val/Met*) functional polymorphism, may be a biomarker for manic symptoms (21), and research has suggested that the effect of this variant may be associated with comorbid manic symptoms in schizophrenia (22). Using the OPCRIT criteria (23), an Irish study showed significant overtransmission of the *Val* allele for mania in patients with schizophrenia (24).

Interestingly, it has been suggested that second-generation antipsychotics, with the exception of clozapine, may induce states of agitation often resembling manic states, possibly via their antidepressant actions on serotonergic and noradrenergic neurotransmission (25).

In the era of promoting health economics through screening (26), we suggest that administering the YMRS, a relatively easy-to-use and cost-effective tool, to screen readily for mania in SSDs may prove a valuable strategy for the busy clinician. YMRS could help identify mania in SSDs, as early intervention may lower the costs of treating poorly responding revolving-door patients (27) and improve patient outcomes (28), thus decreasing costs for the patient and the mental health and welfare systems. Adding mood stabilizers (29) and engaging the patient in psychoeducation (30) may prevent frequent relapses associated with high expenditure for the patient and society.

It is crucial, however, to interpret our findings by considering the various limitations of this study. First, the subjective nature of YMRS introduces inter-rater variability, which could affect the reliability and validity of the assessments. It has recently been suggested that implementing flags and mitigation strategies during trials may enhance the value of YMRS data, direct emphasis toward rater training, and bolster the reliability and validity of trial outcomes (31). Therefore, future YMRS assessments will have to be undertaken by the same trained rater for all patients. This study could serve as a pilot study, as a more representative and larger sample size is required in future studies to enhance data reliability. In the future, genotyping either for known genetic polymorphisms or within a genome-wide association study (GWAS) protocol, without an *a priori* hypothesis, holds promise for disentangling the dimensional etiology of SSDs, part of which seems to stem from the presence of manic symptoms. Another strategy for furthering our understanding of manic symptoms in SSDs may be to focus on patients with drug-naïve first-episode SSD, to eliminate any drug-induced agitation.

Nevertheless, this study highlights that by addressing manic symptoms contributing to and associated with positive psychotic psychopathology in individuals with SSDs, we could improve the management of acute SSD episodes and promote remission, especially in poorly responding patients with undetected, hence suboptimally treated manic symptoms.

Conclusions

This study explored the presence of manic symptoms in patients with SSDs. We showed the severity of positive symptoms to correlate with an increased number of manic symptoms, as assessed by the YMRS. In this group of patients, positive symptoms also predicted the presence of manic symptoms. It, therefore, appears that in SSDs, YMRS could be used as a friendly and reliable screening tool promoting individualized and precision management, increasing the cost-effectiveness of interventions. Further, beyond cross-sectional studies, the high degree of phenomenological pleiotropy within SSDs points to the need for extensive transdiagnostic research to delineate biologically distinct entities incorporating carefully collected phenotypical data from diverse global communities, with the application of new and emerging technologies.

Materials and Methods

Participants

All patients attending the out-patient clinic of the 3rd Psychiatric Department of the Aristotle University of Thessaloniki, aged 18 to 66 years, with an SSD diagnosis, according to DSM-5, were invited to participate. Further inclusion criteria were stable medication for at least 1 month and the absence of any somatic disorder. Recruitment took place between June 2023 and June 2024. All participants signed written informed consent, following approval by the Research and Ethics Committee of the Aristotle University of Thessaloniki (Prot. No. 166/2023, dated 6/6/2023). This study is ongoing as it is part of an international research project involving centers from 22 countries worldwide.

Assessment Tools

We used the YMRS (32), which evaluates the severity of manic symptoms in acute mania and is widely used in clinical trials (33, 34). The scale consists of 11 items based on the patient's subjective reports over the previous 48 h and the examiner's observations during the interview. The selection of each item was based on the published accounts of the key manic symptoms in bipolar affective disorder (35). In this instrument, the irritability, speech, thought content and disruptive/aggressive behavior items are scored from 0 to 8 as they carry greater weight and compensate for poor cooperation in severe cases. The rest are rated from 0 to 4.

In addition, psychopathology was assessed with the PANSS (36, 37). Participants were also required to complete the self-report GAD-7 (38), and the RASS (39). Sociodemographic information for each patient and illness-related factors including current medication, illness duration, age at first episode psychosis, number of attempted suicides, family history of mental illness, total number of episodes, and total number of hospitalizations, were also recorded following interviews with patients and carers and further consultation of medical records, if required.

Study Design/Procedures

Assessment was performed during three sessions on separate days within 1 month. The first session was physician-led and included a thorough medical and psychiatric history taking. The second session, usually no later than a week after the second session, was psychologist-led under the supervision of a psychiatrist. It comprised the clinical interview for assessing psychopathology, including completion of the YMRS, by one of four clinical psychology research assistants. Self-report scales were completed during the third and final session (Figure 2).

Statistical Analyses

All analyses were run using the IBM Statistical Package for Social Sciences (IBM SPSS version 29.0). Descriptive statistics for the whole group were summarized as mean and standard deviation (SD) for YMRS total and individual item scores. We then dichotomized our sample according to YMRS total score setting the cutoff at 10 as suggested previously (14). Using the independent-samples *t*-test, we examined individual item score differences between the dichotomized groups. To examine the statistically significant differences in demographics and the PANSS, GAD-7, and RASS scores between patients diagnosed with SSDs with and without mania, we conducted independent-samples *t*-tests for continuous variables and chi-square (χ^2) tests for categorical variables. Using Spearman's r^2, we also explored correlations between YMRS scoring and PANSS total and subscale scores. Lastly, a linear regression model was developed to measure the association between the severity of positive symptoms according to PANSS total scoring and the presence of manic symptoms. To account for 125 comparisons in total, including the Spearman's correlations (r^2), we used Bonferroni correction by setting the level of significance at $p < 0.05/125$, that is, $p < 0.0004$. *Post-hoc* statistical power was calculated using G*Power version 3.1.9.7 (40) at $\alpha = 0.05$.

Data Availability

Data availability is restricted due to human subject involvement and is non-public. All data used in the analysis are available upon reasonable request to the corresponding author.

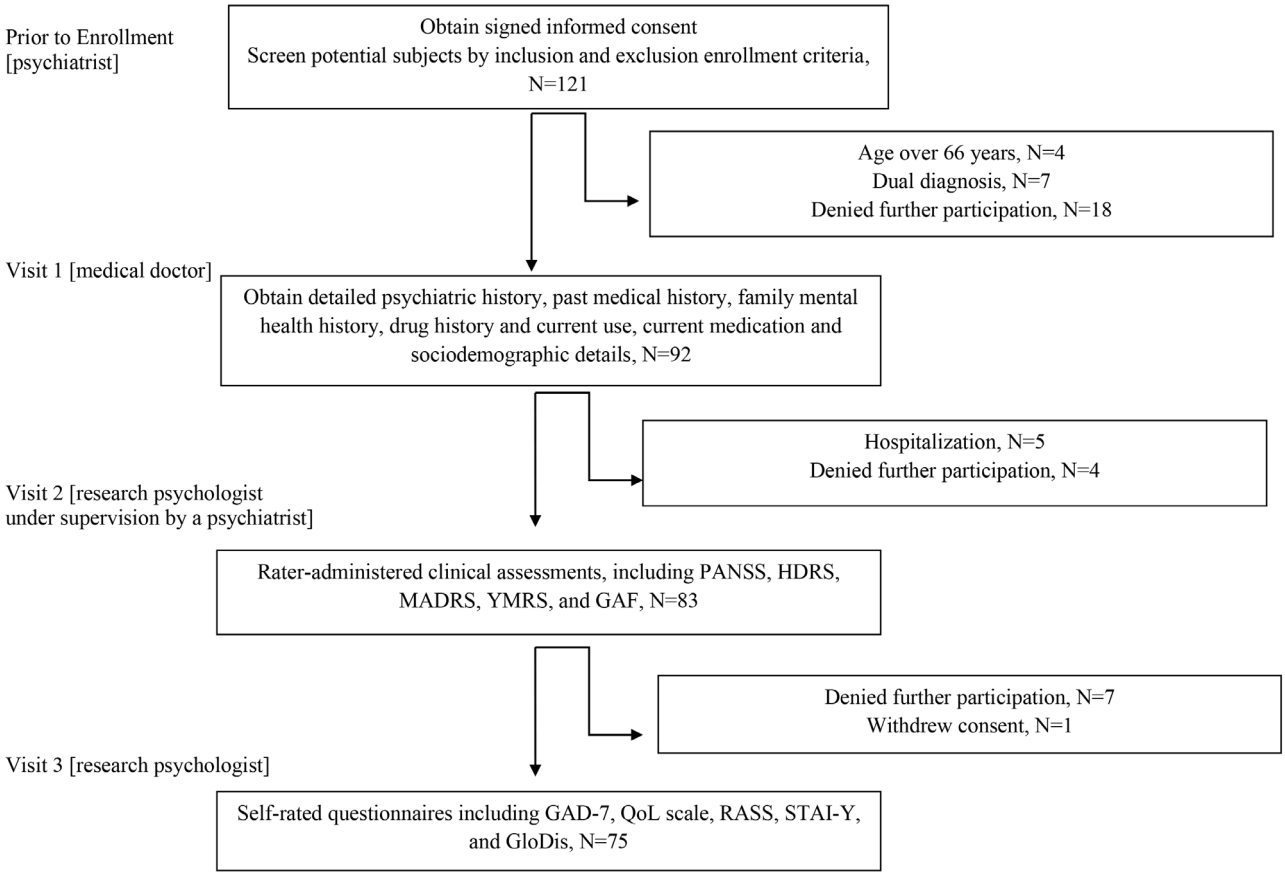

Figure 2. Recruitment flow chart.

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Author Contributions

E.M.T. oversaw clinical research coordination and organized, managed and analyzed the database of results. She was the primary author of the manuscript and orchestrated and contributed to the intellectual conceptualization of the perspective paper; she also participated as a clinical supervisor in data collection. She also acted as research coordinator. D.P. and M.K. conducted semistructured interviews on participants, collected clinical data under supervision and edited the manuscript. K.C. and S.F. collected clinical data and collated relevant data and edited the manuscript. G.K. conducted all primary assessments and screening. K.N.F. conceptualized the research project, was the primary investigator of this study and contributed to the writing and editing of this manuscript.

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Author Disclosures

The authors have confirmed that no conflict of interest exists. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The manuscript has been read and approved by all authors.

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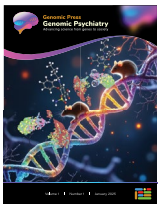

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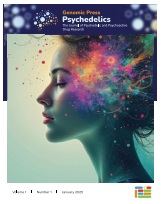

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