Genomic Press
BRAIN MEDICINE
From neurons to behavior and better health

Volume 1 | Number 5 | September 2025

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MARMO-AD
Marmosets as Research Models of Alzheimer's Disease

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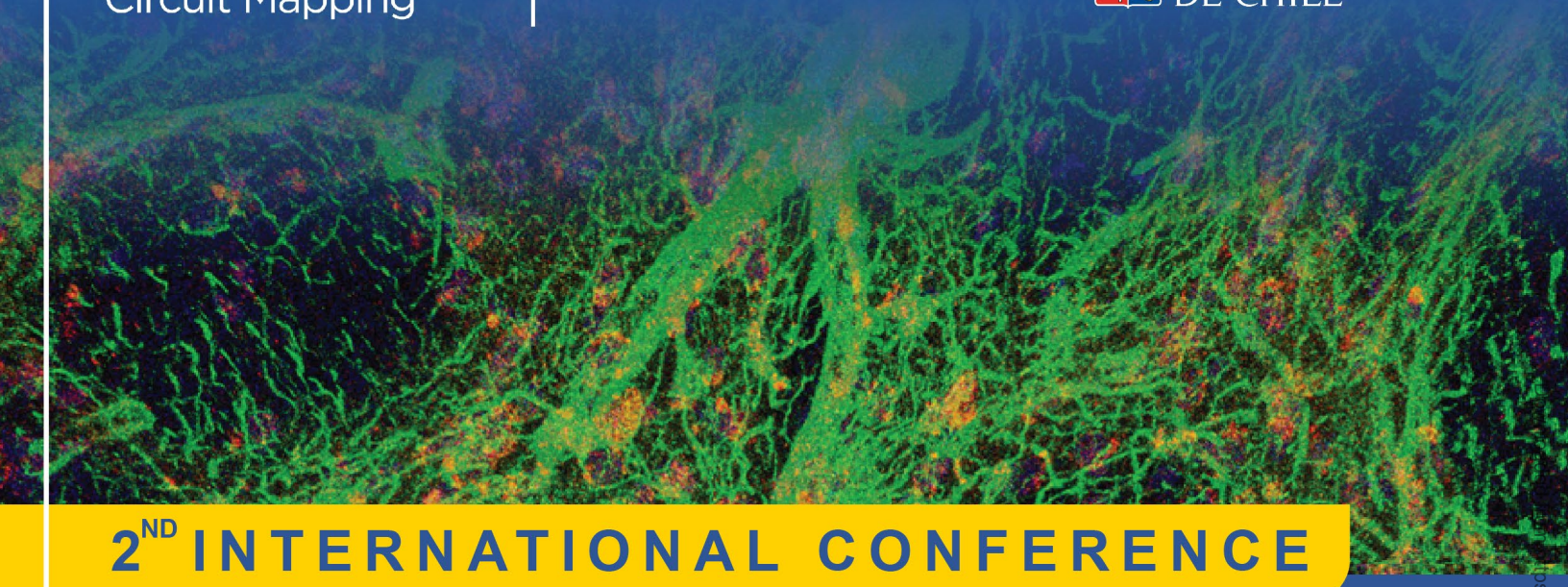

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Brain Medicine is published bimonthly – six times a year by Genomic Press.

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Cover Art

Cover Image: Exercise counters cafeteria diet-induced behavioral despair through metabolic and gut-brain mechanisms. This issue's cover illustrates the interplay between diet, exercise, and mental health investigated by Nota and colleagues. In adult male rats, voluntary wheel running mitigated the increase in immobility (a depression-like behavior) induced by a Western-style cafeteria diet high in saturated fat and sugar. Exercise also exerted modest anxiolytic effects and improvements in spatial learning independent of diet. The antidepressant-like effects of exercise in cafeteria diet-fed rats were accompanied by attenuation of diet-induced increases in plasma insulin and leptin, and restoration of caecal metabolites including anserine, indole-3-carboxylate, and deoxyinosine. Exercise increased circulating GLP-1 and promoted adult hippocampal neurogenesis in chow-fed animals; however, both effects were blunted in rats exposed to the cafeteria diet. Correlation analyses revealed associations between specific caecal metabolites and depression- and cognition-related behaviors, independent of diet and exercise. These findings provide insight into metabolic hormone and gut-derived metabolite mechanisms underlying the effects of cafeteria diet and exercise on brain and behavior, with implications for the microbiotagut- brain axis in mood disorders. Cover image adapted from research by Nota et al. (pages [52–66]) and discussed in the accompanying editorial by Licinio et al. (pages [1–4]).

Image credits: Left panel generated by Grok XAI after extensive human interaction with the editor; right panel by satyrenko via Depositphotos.

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EDITORIAL

Exercise as metabolic medicine: Movement counters diet-induced behavioral despair via gut-brain signaling

Brain Medicine September 2025;1(5):1–4; doi: https://doi.org/10.61373/bm025d.0122

Nowadays, ultra-processed foods that are high in energy are cheaper, more delicious, and more easily available than ever before in human history, as more screens become available and sedentary time increases. At the same time, depression and anxiety are prevalent, enduring, and costly. It is a biological overlap that is manifesting at a macro level, not just a coincidence of modern-day life. If you want to see how these forces interact, check out this preclinical study, which examines the effects of cafeteria food on exercise, behavioral change, hormones, neurogenesis, and changes in gut-derived metabolites.

In their study, "Exercise mitigates the effects of a cafeteria diet on antidepressant-like behaviour associated with plasma and microbial metabolites in adult male rats," published in this issue of *Brain Medicine*, Nota *et al.* provide a detailed, multidimensional view of how lifestyle factors interact (1). Adult male Sprague-Dawley rats at approximately 9 weeks of age were fed either standard chow or a rotating "cafeteria" menu high in saturated fat and sugar. Half of each group had access to a running wheel. Rats were tested for antidepressant-like and anxiety behaviour (forced swim test, elevated plus maze, novelty-suppressed feeding), cognition (spontaneous location recognition, novel object recognition, Morris water maze), adult hippocampal neurogenesis (2), circulating metabolic hormones: insulin, leptin, GLP-1, PYY, FGF-21, ghrelin, C-peptide, glucagon, and an untargeted caecal metabolome panel.

The title is easy to understand and must be stressed: exercise counteracts the cafeteria diet's increase in immobility in the forced swim test. Running pushed behavior in an antidepressant-like direction (reduced immobility in the forced swim test) with junk-style food aboard. This is not a trivial observation. The brain remains responsive to behavioral interventions that we can provide to almost anyone at almost any time, even under adverse dietary conditions.

There is more. Exercise eased anxiety in a conflict-sensitive test. This test was latency to eat in a novelty-suppressed feeding paradigm. The exercised rats also had better spatial learning in the Morris water maze.

On the endocrine front, voluntary running reduced the increases in insulin and leptin caused by cafeteria diets, while increasing GLP-1 and PYY (though with some diet-specific nuances). The cafeteria diet significantly altered the caecal metabolome in the gut, whereas exercise reinstated the abundance of three metabolites that the diet had lowered: anserine, indole-3-carboxylate, and deoxyinosine.

Finally, a different neurogenesis story can provoke great interest: exercise increased doublecortin (DCX)-positive immature neurons in chow-fed rats, but a cafeteria diet blunted that pro-neurogenic effect. It appears that diet quality can influence the functioning of brain neurons during exercise.

When you piece everything together, it depicts what clinicians know

Exercise induces antidepressant-like behavioral effects, even when food is working against us. Exercise supports the metabolic milieu and the gut's metabolome. One route we focus on regarding brain plasticity is adult hippocampal neurogenesis, which appears to be less resilient if your diet is highly processed (3). How can we implement lifestyle prescriptions that are compatible with each other's biology?

The clear signals and the necessary caveats

The cognitive results warrant a measured interpretation, as the effects were modest and mixed in their statistical significance. While exercise improved spatial learning during Morris water maze training (with a significant time-exercise interaction), the probe trial outcomes were less compelling, with only search latency showing clear changes. Pattern separation and recognition memory tasks revealed primarily trends rather than robust effects. This is not a weakness of the study; instead, it provides valuable data showing that an adult-onset cafeteria diet and voluntary exercise do not significantly impact cognitive performance over seven weeks.

The cognitive resilience of adult rats to these interventions contrasts with the more pronounced effects typically seen when similar manipulations begin during adolescence or extend over longer periods (3).

The findings on neurogenesis are the most interesting and significant. We have become very comfortable with a story in which exercise reliably increases adult hippocampal neurogenesis, which in turn leads to improved pattern separation and stress resilience. Here, that is true on standard chow. However, with the cafeteria diet, the DCX increase is blunted. This does not question the exercise-neurogenesis-mood link but refines it in a manner with clinical implications (4). In other words, the condition of the diet may lessen the cellular response we hope exercise will prompt. If you want to use exercise to "rejuvenate" hippocampal plasticity, the surrounding metabolic context matters.

In terms of hormones, the outcomes match up well with clinical experience. A cafeteria diet caused increases in insulin and leptin; exercise attenuated both. This is precisely what we often see in the case of humans who may have diet-induced insulin resistance in response to adiposity. When they increase mobility signals from the periphery, they often normalize before weight changes do. Exercise can increase GLP-1, but this effect is blunted when a cafeteria diet is used. This may be linked to the finding of enhanced neurogenesis, as GLP-1 receptors are known to increase AHN (5). In the cafeteria-diet cohort, exercise increased PYY levels, which possibly contributed to the observed effect. No single hormone explains any behavior, but together they outline a shift in hormonal context, with moderation in amplitude by nutrition, for better central signaling.

The metabolomics data are where this paper opens a door. The cafeteria diet altered the metabolite landscape of the caecum, as amino acid metabolism, tRNA biosynthesis, and the tryptophan pathway were prominent. Exercise did not reverse everything. In fact, exercise appears to only buffer a few key molecules important for the brain, which include the following. Anserine is a histidine-containing dipeptide that has both antioxidant and neuroprotective properties (6). Indole-3-carboxylate is an indole derivative that sits in the broader tryptophan–indole–AhR

Received: 29 September 2025. Accepted: 1 October 2025.
Published online: 21 October 2025.

Figure 1. The metabolic tug-of-war: Exercise versus ultra-processed diet. Voluntary exercise exerts an antidepressant-like behavioral effect and attenuates metabolic dysregulation in rats fed a cafeteria diet. However, diet quality still significantly influences the neuroplasticity response, highlighting the complex interplay between movement and nutrition in brain health. Image Credits: Left panel from Grok XAI; Right panel satyrenko via Depositphotos.

signalling pathway (7). Deoxyinosine is a purine nucleoside with documented links to stress physiology (8). Importantly, the authors do not overclaim. None of these metabolites could predict the behaviour across conditions. Cytosine and other caecal compounds were the stronger correlates of immobility and 5-hydroxyindole-3-acetic acid, 1-phenylethyl acetate, and 4-vinylguaiacol. 2-aminopimelic/aminoadipic acid was negatively correlated with the MSLR cognitive measure. That is precisely what we should expect from a real biological system: many small pushes and pulls, a set of mechanistically tempting candidates, and a web where diet and exercise change the baseline on which those metabolites act.

Just because two things look alike does not mean they are. However, they connect behavioral readouts to measurable molecules in the gut that are modifiable by the two most scalable interventions we have: diet and exercise. That is the start of an actionable biomarker story.

Where does this relate to the clinic?

Clinicians do not treat rats, but we do treat analogous biological processes. Several practical messages emerge.

Exercise has an antidepressant-like effect in the "wrong" dietary context, which is good news for those who have trouble changing their diet. We can say that moving your body helps your brain, even if your diet is not perfect (9). This is particularly applicable in the context of depression, whereby exercise has demonstrated antidepressant effects comparable to first-line treatments such as medications and therapy (10), even with the potential to reduce suicide attempts (11, 12), yet remains significantly underprescribed (12). Although those with depression typically have a poor diet (13), this should not be seen as a barrier to the prescription of antidepressant effects of exercise (14).

Diet quality matters for brain plasticity. When we prescribe exercise, one of our hopes is that it will lead to hippocampal neurogenesis. A heavily processed, high-fat/high-sugar/high microplastic diet may blunt the cellular response (15). This does not mean deferring exercise until the diet is fixed, but rather to frame exercise and diet as partners, not substitutes. Similar to exercise, diet has demonstrated significant associations with depression (16). Particularly, people who consume more ultra-processed foods had a 22% higher risk of incident depression, and those who adhere to a nutrient-dense diet were 30% less likely to have features of depression (17). Beyond this, randomized controlled trials involving people with depression have demonstrated moderate-to-large improvements for those receiving a Mediterranean diet (18). Although most studies have analyzed the Mediterranean diet in relation to depression, there is no single superior diet; any dietary pattern that emphasizes nutrient-dense foods, tailored to individual patient preferences, may be beneficial (19).

Metabolic health is closely tied to mental health (20). Normalization of insulin and leptin levels is associated with improved behavior. On the contrary, insulin resistance is associated with a doubled risk of depression (21). When we help our cells resist insulin, it seems to fix our moods and cognition. It is a reminder to continue screening for metabolic dysfunction in psychiatric care and to take it seriously when we find it.

The gut is not a spectator. Changes in the caecal metabolome (tryptophan derivatives, amino acid catabolites, and dipeptides) are similar to those observed in humans. This similarity provides evidence that gut microbiome-derived metabolites are related to depression and cognitive performance (22, 23). Although we are still sifting through the true mechanism from noise, the broad signal is consistent: the microbiota–gut–brain axis is a lever that plays a crucial role in developing new treatment strategies.

What to build next

The artifacts generated by a good preclinical study should create better questions than it started with. Here are a few that this paper puts squarely on the table.

Do female and older animals behave the same way? Neurogenesis, metabolism, and microbiota composition are influenced by sex and age. Like other studies, this research focuses on males who have reached adulthood. We should now reproduce these efforts with women and test middle-aged and elderly cohorts.

What is the time course and dose response? A reasonable window is seven to eight weeks, but the benefits of diet and exercise accumulate over months, years, or even a lifetime. More prolonged exposure may amplify cognitive effects and neurogenesis. It will also refine metabolite signatures.

Can we restore the neurogenesis response through dietary adjustments? Does targeted dietary improvement (high-fibre intake, availability of tryptophan, low sucrose) restore the pro-neurogenic effect of exercise if a cafeteria diet blunts it? GLP-1 receptor agonists and PYY analogues are now widely used in the clinic; do they induce a normal neurogenesis response on faulty diets?

Which metabolic changes are causal to the interaction between exercise and diet? The paper offers testable candidates such as anserine or indole-3-carboxylate. Efficiently altering aminoadipic acid pathways or 5-hydroxyindoleacetic acid (5-HIAA) in the caecum may also offer insights into causality by providing some behavioural and neurogenic consequences.

How do we translate to humans? The hormones correlate, but the behavioral assays do not. Insulin, leptin, GLP-1, and PYY can be measured before and after supervised exercise in individuals consuming high-sugar/high-fat diets. New non-intrusive ways to measure brain networks through high-resolution fMRI of the dentate gyrus/CA3 combined with cognitive testing may go along with stool metabolomics.

A note on nuance

One approach might be to rephrase a complicated finding into a snappy phrase, such as 'exercise fixes junk food.' The evidence suggests a more subtle and more hopeful one. Exercise induced an antidepressant-like behavioural effect despite junk food. Yes, the quality of a person's diet does impact their brain's deeper plasticity response. There are both unidirectional and bidirectional communication patterns between the gut and the brain.

That nuanced view mirrors people's lived experience. Patients often start moving before they can change their diet. When they feel better, diet becomes more approachable. Increased sleep and less despair lead to a person making a better breakfast. By accepting that the effect size unambiguously depends on the biology, we can design achievable treatment sequences: start with what is doable (walking, stationary cycling, light resistance), stack modest dietary improvements, and let the physiology turn in your favour. We can measure insulin and leptin, not as shaming yardsticks but as early indications that the body is responding.

Why this matters for brain medicine

Psychiatrists and neurologists have long recognized that the brain does not function in isolation. What this paper adds is specificity. The authors show changes in insulin, leptin, GLP-1, and PYY in response to diet and linked them to the antidepressant-like effects of exercise. They showed that a cafeteria diet can suppress hippocampal neurogenesis (new neuron formation), which is elevated after exercise. Finally, they demonstrated that gut metabolites, both endogenous and diet-driven, correlate with behavioral variations. That is work worth chasing. The framework of translational lifestyle psychiatry consists of mechanistic, measurable, and, hence, improvable prescriptions, rather than fuzzy advisories to "eat better and move more."

There is, finally, an ethical dimension. When provided without tools, follow-up, or respect for circumstance, lifestyle change can sound moralizing (24). A paper like this helps us do better. It helps us tell a struggling patient: "Your walks are currently helping you for at least three biological reasons. Your insulin and leptin levels are declining, while your gut generates various compounds, and your brain's mood circuits stabilize. We can make that effect bigger by changing some food, and we will track the biology with you." That is not blame. That is a partnership grounded in physiology.

The take-home

Exercise had an antidepressant-like behavioural effect in adult male rats fed a cafeteria diet. It also produced modest anxiety-reducing effects and cognitive effects.

Exercise has a positive effect on metabolic hormones. GLP-1 and PYY levels increased, whereas insulin and leptin levels decreased. The cafeteria diet blunted some of those gains.

Increased exercise enhanced adult hippocampal neurogenesis; however, this effect was only observed when rats were fed a healthy diet and not a cafeteria diet, suggesting that diet quality can gate plasticity.

The profiles of the caecal metabolome shifted significantly with the diet and selectively with exercise. A handful of metabolites were rescued by running. They include anserine, indole-3-carboxylate and deoxyinosine. Similarly, many other metabolites correlated with behaviour under both conditions.

This is preclinical work, and it should be read as such. However, it conveys a simple yet durable message: the brain remains trainable under metabolic duress; it is possible to be plastic; the gut keeps score; and diet quality moderates the yield of exercise. At the clinic, that means a humane order: help people move first, support metabolic health early on, nudge diet quality up a notch, and monitor their biology when possible. The rest is steady work and time.

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Brain Medicine September 2025;1(5):5–8; doi: https://doi.org/10.61373/bm025k.0086

Keywords: Sonder, aging, Alzheimer's disease, depression, brain, immune system

Dr. Hamilton Se-Hwee Oh is pioneering groundbreaking research at the intersection of neuroscience, immunology, and aging biology at Mount Sinai's prestigious Brain-Body Institute and Ronald M. Loeb Center for Alzheimer's Disease, where he decodes the complex bidirectional communication between the brain and peripheral organs that drives depression, aging, and neurodegeneration. Working under the renowned mentorship of Drs. Scott Russo and Alison Goate, Dr. Oh bridges neuroscience, immunology, and computational biology to decode how psychological stress accelerates organ aging and how peripheral molecular signals rewire neural circuits affecting mood, cognition, and long-term health. His groundbreaking Stanford PhD research in the Wyss-Coray laboratory yielded three first-authored high-impact *publications in Nature* and *Nature Medicine*, including revolutionary discoveries that demonstrated human organs age at differential rates with profound implications for disease susceptibility. Additionally, he identified cerebrospinal fluid synaptic biomarkers that predict Alzheimer's dementia onset years before clinical manifestation. By integrating large-scale human proteomics, single-cell transcriptomics, and mechanistic animal models, Dr. Oh pioneers precision medicine approaches targeting root causes of depression, chronic pain, and age-related neurodegenerative diseases. His innovative research examines how immune cells and metabolic organs amplify or dampen mood symptoms, utilizing cutting-edge metabolomic and proteomic profiling to identify peripheral proteins and metabolites that track depressive behavior. Currently investigating the molecular fingerprints of interventions such as exercise and ketamine, Dr. Oh's multidisciplinary approach positions him at the forefront of developing next-generation therapies. His work exemplifies how young scientists can leverage big data and systems biology to transform our understanding of brain-body interactions, offering hope for millions suffering from neuropsychiatric and neurodegenerative disorders worldwide.

Figure 1. Hamilton Se-Hwee Oh, PhD, Icahn School of Medicine at Mount Sinai, USA.

Part 1: Hamilton Oh – Life and Career

Where were you born, and where do you live now?
I was born in North Carolina, USA. I now live in New York City, New York, USA.

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?
I grew up in Connecticut as an active kid who loved playing outdoors, whether in the water, snow, or piles of autumn leaves, depending on the season. At school, my favorite subject was math, and at home, I spent hours building with Legos and playing video games. My interest in biology began to take shape in high school, when I became more reflective about my own life and the lives of those around me, especially after learning the concept of *sonder* in my humanities class: the realization that every person lives a life as vivid and complex as our own. It amazed me that this rich, emotional, subjective experience could arise from the coordinated activity of trillions of cells. What ultimately drove me to study biology in college, though, was personal experience. I was diagnosed with a rare chronic kidney disease (which, fortunately, remains stable today), and I watched my best friend develop a persistent, unexplained abdominal pain that continues to affect his life. I hoped that by studying the intricate inner workings of life, I might one day contribute to curing the kinds of conditions that cause such deep and often invisible suffering.

Please share with us what initially piqued your interest in your favorite research or professional focus area.
As an undergraduate at the University of California, Los Angeles (UCLA), I was drawn to the promise of stem cell research and its potential to revolutionize treatments for degenerative diseases. Around the same time, I kept encountering references to "inflammation" across a wide range of diseases, from cancer to heart disease, which led me to think that studying the immune system's stem cells, hematopoietic stem cells, could be a promising direction. This curiosity brought me to Hanna Mikkola's lab,

Received: 12 July 2025. Accepted: 15 July 2025.
Published online: 22 July 2025.

where I investigated how specific transcription factors regulate the development of hematopoietic stem cells during embryogenesis in mice. While I found the study of intracellular mechanisms governing stem cell identity fascinating, I became increasingly intrigued by the role of the surrounding microenvironment, the stem cell niche, and how external cues from neighboring cells influence stem cell development and function.

This interest led me to pursue a PhD in Stem Cell Biology and Regenerative Medicine at Stanford University, where I initially set out to study how the adult bone marrow niche regulates hematopoietic stem cells during immune system regeneration. But as often happens in science, my interests evolved. During a rotation in Tony Wyss-Coray's lab, I became captivated by the interplay between the immune system and the brain in the context of aging and Alzheimer's disease. I began by culturing neurons with T cells to explore their interactions and later analyzed single-cell transcriptomes from immune cells in the cerebrospinal fluid of Alzheimer's patients.

I was excited by the opportunity to study human disease directly, especially at a time when high-throughput molecular profiling technologies were offering unprecedented resolution into human biology. I also rediscovered my fascination with the brain, the organ central to emotion, consciousness, and self, concepts that had first sparked my interest in biology during high school. At the same time, I realized that aging itself is a powerful upstream driver of many chronic diseases and that understanding it could offer broad insights into disease prevention and healthy longevity.

I ultimately joined the Wyss-Coray lab for my thesis work, where I continued my research in Alzheimer's immune system single-cell transcriptomics (Oh H., et al. *Molecular Neurodegeneration* 2021, DOI: 10.1186/s13024-021-00423-w) while also expanding into large-scale human plasma and cerebrospinal fluid proteomics to study how humans age (Rutledge J., Oh H., and Wyss-Coray T. *Nature Reviews Genetics* 2022, DOI: 10.1038/s41576-022-00511-7). We discovered that our internal organs age at different rates, and this has consequences for our susceptibility to age-related diseases, ranging from heart disease to Alzheimer's dementia (Oh H.S.-H. and Rutledge J., et al., *Nature* 2025, DOI: 10.1038/s41586-023-06802-1). We also found that the brain and immune system were key organs linked to long-term health and longevity in humans (Oh H.S.-H., et al. *Nature Medicine* 2025, DOI: 10.1038/s41591-025-03798-1). Lastly, we identified a pair of synaptic proteins in human cerebrospinal fluid whose levels could predict if and when someone would develop Alzheimer's dementia (Oh H.S.-H., et al. *Nature Medicine* 2025, DOI: 10.1038/s41591-025-03565-2).

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 found the scale and human impact of my PhD research fascinating and rewarding. At the same time, I felt frustrated at its largely correlative nature, which limited our ability to draw causal conclusions. This motivated me to return to the animal model experiments that first drew me to lab science so I could investigate the mechanisms underlying brain-immune system interactions in aging and Alzheimer's disease. I also felt a pullback to my original interests from high school of understanding the subjective human experience and working to treat conditions like chronic pain, which may not shorten lifespan but profoundly diminish the quality of life.

After exploring the literature and engaging in numerous conversations with scientists across various fields, I found a home for my interdisciplinary interests at the Brain-Body Institute and the Loeb Center for Alzheimer's Disease at the Icahn School of Medicine at Mount Sinai. As a postdoctoral fellow co-advised by Scott Russo and Alison Goate, I am currently pursuing several projects on brain-immune interactions in chronic stress, depression, and dementia, which span both animal models and human participants, including ongoing clinical trials. I am particularly interested in how psychological stress accelerates aging in peripheral organs and how signals from these organs can, in turn, rewire the brain to shape our emotional states and long-term health.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

Switching fields in graduate school from hematopoietic stem cell biology to Alzheimer's disease and aging felt quite risky. I was not a neuroscientist, and I had no prior experience with bioinformatics, so the first two years in the lab were a period of considerable exploration, especially during the COVID-19 pandemic. I struggled with self-doubt and often felt lost. However, one silver lining of the pandemic was that it provided me with the opportunity to focus intensely on learning how to code and apply what I learned in class to explore our lab's human omics datasets. I enrolled in Stanford's undergraduate courses in Programming Methodology, R for Biostatistics, and Linear Algebra over my first year, which was invaluable. I never liked programming in college because I lacked a clear purpose for it, but in graduate school, using programming to explore questions about Alzheimer's biology was so fun and exciting! When my plasma proteomics project on human organ aging began to show real promise, I decided to fully commit to it, a decision that ultimately transformed my scientific trajectory.

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

Over time, I have come to realize that it is difficult to commit to something that does not genuinely excite me fully. Even if a project is objectively important and interesting, if it does not resonate with me, it does not receive the attention it deserves. I have made a point to pursue projects that naturally spark my curiosity, and as a result, I find myself working harder without even realizing it.

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

I am currently focused on dissecting the bidirectional communication between the brain and peripheral organs in the context of chronic stress and depression. Major depressive disorder is not simply a disorder of the central nervous system; it is increasingly evident that immune cells and metabolic organs like the gut can amplify or dampen mood symptoms. Using large-scale proteomic and metabolomic profiling of blood from both patients and mouse models, I hope to identify peripheral proteins and metabolites whose levels track with, or precede, depressive-like behavior. I aim to test whether specific candidates emerging from these screens are causal in depressive-like behavior. Moreover, I am examining the molecular "fingerprints" of natural and pharmacological interventions, such as exercise and ketamine, to uncover mechanisms that can promote recovery from and resilience to chronic stress.

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

Ultimately, I hope these studies reveal novel mechanisms of brain-body communication that we can leverage to develop new therapies for diseases of human suffering.

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

I appreciate that academia values intellectual freedom, the ability to pivot toward new leads, and the opportunity to learn new skills, even if this means lower productivity during the early stages of a project. I am deeply grateful to my advisors for investing in my growth and learning.

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 you feel strongly devoted to?

As scientists, we celebrate those who think outside the box and make groundbreaking, unexpected discoveries. Yet, most funding agencies

Figure 2. Early days, imagining life from millennia ago. American Museum of Natural History, New York, USA. Sunday, 25 December 2005.

prioritize proposals backed by substantial preliminary data and that are relatively incremental in scope. Because researchers generally focus on what is funded, funding institutions must rethink their priorities. Supporting more high-risk, high-reward projects, especially from early-career investigators, could be genuinely transformative.

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?
Having recently moved to New York City, I have enjoyed exploring the vibrant food scenery. I love NY pizza and bagels! I also like jogging around Central Park, playing pickleball, and going to the movies.

Part 2: Hamilton Oh – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
Tall Korean boy.

Among your talents, which one(s) give(s) you a competitive edge?
Comfort in wandering, intense focus, friendly.

If you could change one thing about yourself, what would it be?
Less shy.

What is your current state of mind?
Excited to start something new.

What is your idea of perfect happiness?
Nature adventure, good food, and laughs with loved ones.

When and where were you happiest? And why were so happy then?
Being on a dance team in college. Community, abstract self-expression, physical fitness, and a high metabolism allowed me to eat a lot.

What is your greatest fear?
No love.

What is your greatest regret?
Not yet a regret because I still have time, but I wish I could play blues solo on the electric guitar.

What are you most proud of?
Living true to my values.

What do you consider your greatest achievement?
Doing and sharing science that people find valuable.

What or who is your greatest passion?
There are too many to pick from.

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

What is your greatest extravagance?
High-quality extra-virgin olive oil and tomatoes from Italy.

What is your most treasured possession?
My box of memories.

Where would you most like to live?
I do not know yet. But I miss California.

[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.

https://doi.org/10.61373/bm025k.0086

What is the quality you most admire in people?
Authenticity, kindness, leadership, humor.

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

What do you consider the most overrated virtue?
Efficiency.

What do you most value in your friends?
Laughing together.

Which living person do you most admire?
The many people who work selflessly to make the world a better place.

Who are your heroes in real life?
My friends and family.

If you could have dinner with any historical figure, who would it be and why?
John Mayer is an amazing guitarist/singer/songwriter.

Who are your favorite writers?
Haruki Murakami and Roald Dahl.

Who are your heroes of fiction?
Spiderman and Anakin Skywalker.

What aphorism or motto best encapsulates your life philosophy?
Figure out what you want to do before what you want to be. Play with the data. Have fun.

New York, New York, USA
12 July 2025

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Brain Medicine

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INNOVATORS & IDEAS: RESEARCH LEADER

Illana Gozes: From the pivotal discovery of activity-dependent neuroprotective protein (ADNP) through its investigational drug davunetide: brain molecular medicine providing hope for autism, schizophrenia, and Alzheimer's disease

Brain Medicine September 2025;1(5):9–12; doi: https://doi.org/10.61373/bm024k.0088

Keywords: Regulation of gene expression, tubulin, microtubules, tauopathy, neuropeptides, VIP

Professor Illana Gozes, Ph.D., is a faculty member at Tel Aviv University. Formerly holding the Lily and Avraham Gildor Chair for the Investigation of Growth Factors, she now directs the Dr. Diana and Zelma Elton Laboratory for Molecular Neuroendocrinology. A world-renowned neurochemist, Professor Gozes currently serves as the President of the European Society for Neurochemistry and Vice President of Drug Development at ExoNavis Therapeutics Ltd. Her groundbreaking research began in the late 1970s and early 1980s when she discovered multiple tubulin forms within a single neuron. She demonstrated that these forms evolve with brain development, play a crucial role in synapse formation, and can be identified using monoclonal tubulin antibodies. At the forefront of molecular neuroscience in the 1980s, Professor Gozes became the first to clone the gene encoding vasoactive intestinal peptide (VIP), a key regulatory neuropeptide in the brain. Her research revealed increased VIP expression during synapse formation. In her quest to identify proteins activated by VIP and facilitate neuro-glial interaction, the Gozes laboratory discovered and cloned a novel protein: activity-dependent neuroprotective protein (ADNP). Subsequent research established ADNP's essential role in brain formation and function. Through a series of highly cited articles, Professor Gozes demonstrated that ADNP regulates thousands of essential genes during brain development in a sex-dependent manner and associates with an intricate array of vital proteins. She uncovered ADNP's key role in autophagy and schizophrenia, revealed a fundamental shared mechanism in autism involving critical binding of ADNP with SHANK3 and actin, and showed ADNP's regulation of microtubule dynamics and Tau interaction, which protects against tauopathy. Furthermore, she discovered somatic mutations in ADNP and related genes in Alzheimer's disease, paralleling tauopathy. Her pioneering work on ADNP-deficient mouse models predicted the ADNP syndrome, an autistic/intellectual disability syndrome driven by de novo mutations in ADNP and presenting with tauopathy. Professor Gozes took a reductionist approach to discover an active site in ADNP, leading to the development of the investigational drug davunetide (NAP). This compound has shown promise in protecting against ADNP deficiency/mutations in animal models and in clinical trials. It has been tested in women suffering from progressive supranuclear palsy (PSP), a pure tauopathy, and in individuals with prodromal Alzheimer's disease, demonstrating effects in a sex-dependent manner. Further promise was shown in schizophrenia patients, suggesting improvement in real-world problem solving and task performance. We are honored that Professor Gozes has agreed to share her life's journey with our readers in this Genomic Press Interview.

Figure 1. Illana Gozes, PhD, Tel Aviv University, Israel.

Part 1: Illana Gozes – Life and Career

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

I was born and raised in Jerusalem, Israel, my late grandfather (Menahem Mendel Haltovsky) was a medic with a catching love and passion for providing help to his patients. In primary school, equipped with a microscope and books about renowned scientists, I was very interested in finding out how things worked. I liked mathematics and took it as a major at my prestigious high school. However, my late father (Isac Allon), who was a civil engineer, convinced me that solving nature needs more than mathematics. The heart of Jerusalem at that time was the Hebrew University and the Parliament House. I was not drawn to politics but was inspired by the intellectual spiritual nature of the beautiful city of Jerusalem and admired academics in the field of biology and medicine. I chose Tel Aviv University, then a young and aspiring university close to the tranquil Mediterranean beach, for my under graduate studies and loved every moment of my studies. At the time of my graduation, the Weizmann Institute of Science started a direct Ph.D. program for the best students in biology country-wise. I was amongst the chosen 16 students and neurochemistry became my life passion, the molecular understanding of the brain toward helping humanity to fight brain diseases.

Received: 26 September 2024. Accepted: 26 September 2024.
Published online: 4 October 2024.

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

As a young undergraduate and graduate student, I was extremely interested in my experiments and my results, always enchanted by new techniques and new problems. It became clear to me that it is of the utmost importance to share one's knowledge, either in lectures or in writing. My first paper, published in the Proceedings of the National Academy of Science (USA) entitled: "Translation in vitro of rat brain messenger RNA coding for tubulin and actin" combined both the strive to understand the intricate function of the brain at the molecular level and the grasp of the importance of sharing knowledge to move forward. As such, I was fortunate to participate in the birth of the then a new field, molecular neuroscience. In one of my papers, accepted w/o any changes, we discovered tubulin and actin synthesis in brain cell nuclei, a very new and exciting finding back then. I think that my persistence and hard work ethics channeled me toward leadership and responsibilities coupled with the passion for sharing and openness to collaborative work. Some of my best friends are my work colleagues, and my lab personnel represent my extended family members.

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

Marie Curie findings, the discovery of the DNA structure, the double helix, the discovery of the need for sterilization, and my first lecture abroad at the Laboratory of Professor Rita Levi Montalcini in Rome, all crystallized my passion for molecular neuroscience. Our cloning of the VIP gene and developing the first transgenic mouse model for VIP, showing learning deficiencies further led me to new discoveries. A most appropriate example, is our identification of ADNP and our investigational drug, davunetide, from gene to behavior and to clinical development. In the early 1980's, I named one of my first grant proposal "From Gene to Behavior" and was awarded for it, by the President of the State of Israel, the first Bergmann Memorial Award for the best grant proposal amongst the US-Israel Binational Science Foundation young applicants.

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

I hope to be able to further understand the mechanism of brain development and aging, leading to better insights on brain diseases, which will allow for better diagnostic measures. I am proud of my work on oral microbiota signatures in post-traumatic stress disorder (PTSD) veterans, published in *Molecular Psychiatry* (2022), with findings complementing discoveries made by the team with Julio Licinio and colleagues in China in the laboratory setting, describing the biogeography of the large intestinal mucosal and luminal microbiome in cynomolgus macaques with depressive-like behavior, originally published in *Molecular Psychiatry* (2021). I further connected microbiota signatures to the autistic/intellectual disabilities ADNP syndrome by in depth characterization of my genetically engineered and genome edited mouse models, toward better diagnosis and most importantly better therapeutics. Focusing on therapeutics, I strive to bring our ADNP-derived investigational drug, davunetide and related compounds providing neuroprotection to affected individuals, turning deep understanding of molecular brain function to medical/societal impact. Here, a major concentrating effort is made on ADNP syndrome children, first collected as a group of 10 children led by Belgian and US scientists and defined as a syndrome, driving increased excellent interest in ADNP and beyond.

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

I am very intrigued by the similarities between delayed/aberrant brain development, as in the case of the ADNP syndrome as well as tubulinopathies, and neuropsychiatric diseases like schizophrenia associated with microtubule dysfunction and neurodegenerative diseases with an underling tauopathy. My first love in science was the protein tubulin and my continuous quest for the understanding of the brain led me to discover a new microtubule – interacting protein, ADNP. I focus on better understanding of ADNP in the realm of brain development and aging with great interest in sex differences, given my recent findings on unexpected gender differences in progressive supranuclear palsy revealing efficacy for davunetide in women (*Translational Psychiatry*, 2023) and sex-dependent boosting of memory in prodromal Alzheimer's disease (*Translational Psychiatry*, 2024).

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

I engulf myself with work, making precise plans, but open for changes depending on findings. I cherish my dedicated students and collaborators, always striving to work with the best of the best. I have learnt early on from my PhD mentor the late Uriel (Uri) Littauer to share my findings in scholarly publications, which I continued on doing with my postdoctoral fellow mentor, the 2021 Brain Prize winner, Michael (Mike) Moskowitz at MIT who gave me complete freedom to work, collaborate and publish coupled with students, postdoctoral fellows and a technician. For example, Gozes and Sweadner, Multiple tubulin forms are expressed by a single neurone (*Nature*, 1981), & Gozes and Barnstable, Monoclonal antibodies that recognize discrete forms of tubulin (*Proc Natl Acad Sci USA*, 1982). The head of the MIT section at that time, Richard Wurtman passed away recently and together with my recent MSc graduate Yael Toren (his granddaughter), we dedicated one of my latest papers to his memory: Sex-Specific ADNP/NAP (Davunetide) Regulation of Cocaine-Induced Plasticity (*J Molecular Neuroscience*, 2024).

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

I think science has no borders, the passion for knowledge and communication brings people together. I enjoy promoting the young and as such, in my capacity as the President of the Israel Society for Neuroscience (2008–2010) I strived to establish the Israel Brain Bee Competition, I set up the Tel Aviv Chapter of the Society for Neuroscience (US) and later founded the Israel Brain Bee initially together with Dr. Tal Iram, the Davidson Institute at the Weizmann Institute of Science and the Youth University at Tel Aviv University. The competition is now running with the support of the Israel Ministry of Education. In the alphabetic organization of the competition, Israel sits side by side with Iran and Italy. These young high school students are equally interested in the brain, I wish for them to inherit a peaceful world.

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

Working and solving problems (I wish I could solve more), publishing and having my work acknowledged and appreciated by others, such Douglas (Doug) Brenneman who was indispensable in our discoveries of activity-dependent neurotrophic factor (ADNF) and later ADNP and Mati Fridkin, my initial VIP collaborator as well as Julio Licinio, inviting my interview, appreciating my works for publication and citing them in his review: "Advances in autism research, 2021: continuing to decipher the secrets of autism". I enjoy writing and interacting with brilliant fellow scientists, I feel science has no age differences. It keeps us young and always striving to be better.

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, my husband, Yehoshua, our daughter, Adi, her husband Amir, and our three gifted grandchildren, Tom, Emma and Daniel. I love to watch all of them grow and thrive, playing chess, much better than me, solving math and logical problems and just loving them. I am extremely fortunate and proud to have them.

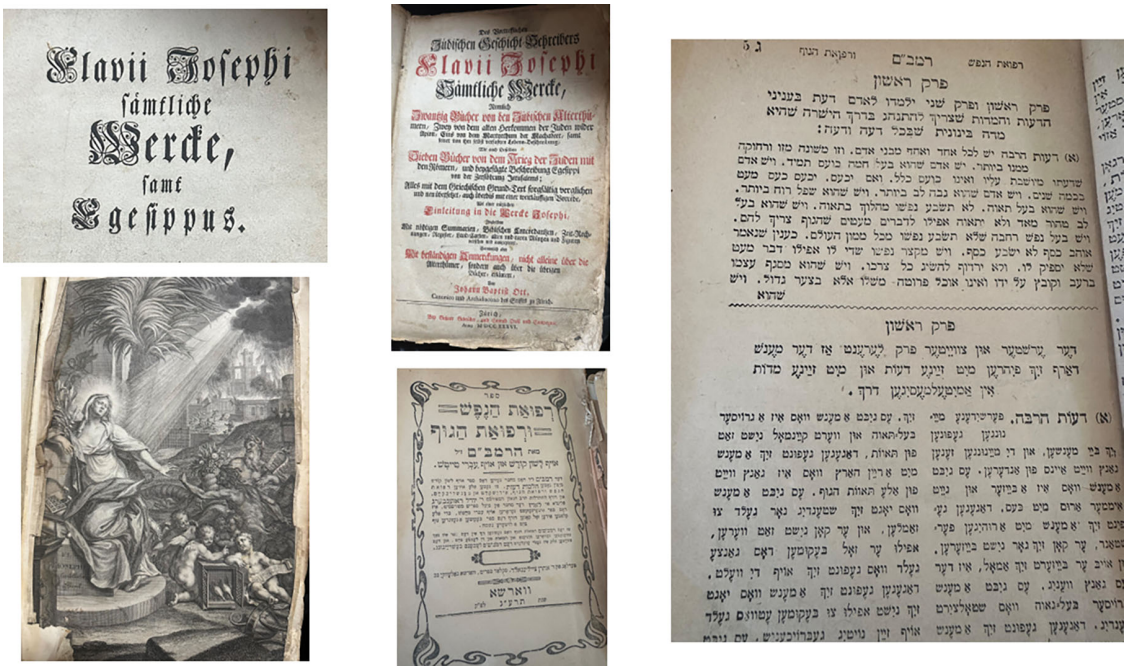

Figure 2. Treasured Possessions. Two written pages and a picture from Josephus Flavious book (a collection) as well as the first and second pages of Maimonides – Medicine for the Body and Medicine for the Soul, in Hebrew and Yiddish. The Maimonides book cover page is depicted followed by the first chapter, saying that people, opinionated as they may be, should behave honestly and always strive to find a middle peaceful way.

Part 2: Illana Gozes – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Love your fellow human being as you love yourself.

What is your greatest fear?
If there is a will, there is a way, I do my best to put my fears aside.

Which living person do you most admire?
My family, my daughter, Adi Gozes – Hamenahem, for being there with me.

What is your greatest extravagance?
Traveling to scientific and business meetings, giving plenary talks and receiving medals (Fogarty-Scholar-in-Residence, NIH, USA) and multiple international awards for research achievements.

What are you most proud of?
Receiving the Champion of Hope Award by Global Genes, recommended by the ADNP parents, for my discovery of ADNP and davunetide: my dream is to help this community!

What is your greatest regret?
The hatred of neighbors, I wish all the money spent on ammunition will be spent on science, health and peace, I wish I could help world peace. There is a place in the world for everyone.

What is the quality you most admire in people?
Love, intelligence, and honesty.

What is the trait you most dislike in people?
Hate, bigotry, and dishonesty.

What do you consider the most overrated virtue?
Beauty and success, these are traits judged by the eyes of the beholders.

What is your favorite occupation (or activity)?
Working and writing science and seeing family and friends.

Where would you most like to live?
My home is my castle, I love my home in a small town just outside Tel Aviv, where strawberry fields are mixed with friendly small town urban life.

What is your most treasured possession?
I treasure two books: one of them contains Josephus Flavious writings on the history of the Jews; that is my father's family's heirloom, which we estimate to have been printed around 300 hundred years ago. The other volume is my grandfather's used Maimonides – *Medical Book*, which we know to be over 100 years old (see Figure 2).

When and where were you happiest? And why were so happy then?
At the birth of my only daughter, I cherished the miracle of life.

What is your current state of mind?
Enjoying writing this article and hoping for peace.

What is your most marked characteristic?
The love for work.

[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.

Among your talents, which one(s) give(s) you a competitive edge?
Persistence, curiosity, scientific logic as well as long-term memory.

What do you consider your greatest achievement?
The original discovery, cloning and characterization of ADNP and davunetide, which followed on the original cloning of the VIP gene and the discovery of multiple tubulin subunits in the single neurons, in short, discoveries of molecules that make our minds.

If you could change one thing about yourself, what would it be?
To better understand my fellow human beings and strive for friendship.

What do you most value in your friends?
Compassion and intelligence.

Who are your favorite writers?
Rudyard Kipling, Oscar Wilde, George Bernard Show, Lord George Gordon Byron, Robert Frost, and the Israeli poet, Rachel.

Who are your heroes of fiction?
As a child I liked the story of Hans Brinker or The Silver Skates. I equally liked the characters of Little Women, and my heart ached with the story of the Scarlet Letter. I also like the detectives in Agatha Christy novels as well as Sherlock Holmes and Dr. Watson

Who are your heroes in real life?
Except for my family members, students and collaborators mentioned above, my heroes are my generous supporters and believers of my research, Ephraim (Ephi) Gildor, the Elton family, Ronith and Armand Stemmer, Arie Dubson, Chair A.M.N. Foundation, the late Marcel Adams and his son Sylvan, Holly and Jonathan Strelzik as well as Anne and Alex Cohen. In therapeutics development, I cherish my business partners starting from Allon Therapeutics and now ExoNavis Therapeutics Ltd with its excellent staff, led by Gabriel Eldor and Yoram Drucker. As I have had about 100 trainees, I cannot name them all or exhibit favoritism, but I am very proud of their progress and attainment of prominent positions, like chairing universities, companies, and hospital departments. On my mother's side of the family, I am fascinated by my ancestors, Abraham Senior (Segovia 1412–1493) (later named Coronel) a Jewish rabbi who was a leading tax farmer in Spain and had to convert to Christianity in 1492. His descendant, Nachman Nathan Coronel (1810–1890) was a Jerusalemite Jewish scholar building his home in Jerusalem as a young man for his descendants including me.

What aphorism or motto best encapsulates your life philosophy?
1] Rudyard Kipling: "If you can keep your head when all about you are losing theirs and blaming it on you..."
2] Robert Frost: (a) "Two roads diverged in a yellow wood and I – I took the one less traveled by and that has made all the difference." (b) "The woods are lovely, dark and deep, but I have promises to keep, and miles to go before I sleep..."

Illana Gozes[1]
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INNOVATORS & IDEAS: RESEARCH LEADER

Ana Cristina Andreazza: Driven by curiosity – transforming mental health through mitochondrial innovation

Brain Medicine September 2025;1(5):13–16; doi: https://doi.org/10.61373/bm024k.0112

Keywords: Mitochondrial health, mental health, metabolic psychiatry, innovation, personalized medicine

Dr. Ana Cristina Andreazza is a Professor of Pharmacology Toxicology and Psychiatry at the University of Toronto, holding the Thomas C. Zachos Chair in Mitochondrial Research and a Tier II Canada Research Chair in Molecular Pharmacology of Mood Disorders. As the visionary Founder and Scientific Director of the Mitochondrial Innovation Initiative (Mito2i), she leads pioneering research on the role of mitochondrial dysfunction in neurological and psychiatric diseases, organ transplants, and novel therapeutic strategies. Her groundbreaking work has revolutionized our understanding of the relationship between mitochondrial function and mental health disorders, particularly bipolar disorder. Dr. Andreazza's career was inspired by early curiosity, family influence, and a commitment to reduce the stigma surrounding metabolic and psychiatric conditions. Her innovative work bridges multiple disciplines, aiming to discover biomarkers that could enable personalized treatments in mental health. A recipient of numerous prestigious awards, including membership in the Royal Society of Canada College of New Scholars, Dr. Andreazza has published over 200 peer-reviewed papers and is internationally recognized for her contributions to metabolic psychiatry. In this Genomic Press Interview, she shares insights into her remarkable journey from studying wine chemistry in Brazil to becoming a leading force in mitochondrial research while discussing her perspectives on collaborative science and innovation. Driven by a passion for teaching and collaborative science, Dr. Andreazza continues to foster innovation and mentorship in the mitochondrial research community.

Figure 1. Ana Cristina Andreazza, Pharm, PhD, University of Toronto, Canada

Part 1: Ana Cristina Andreazza – 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 began my career as a pharmacist, transitioning to science to explore the antioxidant properties of flavonoids at the Biotechnology Institute at the University of Caxias do Sul, Brazil. This exploration ignited my interest in the redox mechanisms in the brain and propelled me toward graduate studies in Biochemistry. For my doctoral thesis, I investigated how oxidative stress contributes to major psychiatric disorders, such as bipolar disorder and schizophrenia. In 2008, I furthered this research during a postdoctoral fellowship at the University of British Columbia, where I studied oxidative damage to specific mitochondrial proteins in the prefrontal cortex tissue of patients with these conditions. Throughout my education, I was fortunate to learn from exceptional mentors who profoundly influenced my passion for both teaching and discovery, guiding me to cultivate my communication skills through speaking engagements and mentoring others.

However, my interest in science started even earlier. My grandfather's family challenge captivated me: "Why does this wine taste so bad?" This curiosity led me, at a young age, to knock on the door of Professor Mirian Salvador, a local researcher studying resveratrol, with a simple request: "Could I study resveratrol?" Driven by my grandfather's winemaking woes, I wanted to explore the connection between the grape compound and the taste of his wine. Professor Salvador, without hesitation, welcomed me into her lab and exposed me to critical thinking, a deep appreciation for mitochondrial metabolism, and a love for scientific inquiry. This early experience left an indelible mark on my approach to science and leadership.

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?

A defining moment in my career came in 2014 during a webinar where a mother whose son have bipolar disorder—and who had also lost two children to mitochondrial disease—reached out to ask if these two conditions were connected. Her question motivated me to work with her family, which led to discovering similar families worldwide. This marked the birth of a new research area that required extensive collaboration across diverse fields. This experience inspired me to establish the Mitochondrial Innovation Initiative (Mito2i)—a network of researchers, clinicians, patient advocates, and partners committed to transforming our understanding of mitochondrial function in health and disease.

Today, as a Professor in the Departments of Pharmacology & Toxicology and Psychiatry at the University of Toronto, I hold the Thomas C. Zachos Chair in Mitochondrial Research and a Tier II Canada Research Chair in Molecular Pharmacology of Mood Disorders. I am also the Founder and Scientific Director of Mito2i, a Senior Fellow at Massey College, a Member of the Royal Society of Canada College of New Scholars, and serve on the

Received: 30 October 2024. Accepted: 1 November 2024.
Published online: 7 November 2024.

Bipolar Scientific Steering Committee for BD2: Breakthrough Discoveries for Thriving with Bipolar Disorder and member of Metabolic Mind. These roles allow me to lead research on mitochondrial function in neurological and psychiatric disease, organ transplant, and novel therapeutic strategies while nurturing an inclusive environment for scientific discovery.

Please share with us what initially piqued your interest in your favorite research or professional focus area.
My family shaped my career path. My mother, a brilliant teacher, devoted her life to public service, empowering those with fewer opportunities. Her dedication inspired me to pursue a career in academia. My father, a mathematician and professor of statistics, possessed an insatiable curiosity but struggled with untreated metabolic psychiatric issues. His journey fueled my commitment to identifying biomarkers that could demystify and reduce the stigma surrounding such conditions. This combination of academic influence and personal motivation solidified my drive to research metabolic psychiatry and the link between mitochondrial dysfunction and mood disorders.

What impact do you hope to achieve in your field by focusing on specific research topics?
My goal is to identify biomarkers that can pave the way for personalized treatments in metabolic psychiatry. Mitochondrial dysfunction is increasingly recognized as a root factor in metabolic syndrome, linking cellular energy regulation with metabolic homeostasis. For example, acetyl-CoA produced by mitochondria initiates cholesterol synthesis, underscoring mitochondria's role in lipid biosynthesis. When mitochondrial function is compromised, cells may shift to anaerobic glycolysis, leading to glucose intolerance and insulin resistance, both prevalent in mood disorders. By uncovering how disrupted metabolism influences disease, I aim to improve treatments, reduce patient suffering, and alleviate healthcare costs associated with ineffective therapies.

Please tell us more about your current scholarly focal points within your chosen field of science.
My research integrates three interconnected areas of mitochondrial science. First, I focus on understanding mitochondrial impairments in mood disorders, particularly bipolar disorder. Using brain organoids derived from patient stem cells, we study the dysregulation of complex I genes, elevated reactive oxygen species, and reduced NDUFS7 expression. This work aims to identify novel therapeutic targets that could restore mitochondrial function and neurotransmission, potentially transforming mood disorder treatment.

In our second research stream, we explore mitochondrial health in organ transplantation, with a particular focus on lung transplants. Our goal is to enhance mitochondrial preservation to improve post-transplant outcomes and reduce complications. We have recently expanded this work to address ischemic and heart injury, taking a multidisciplinary approach to regenerative medicine.

The third area involves a large collaborative network pioneering work in mitochondrial transplantation. We are developing innovative approaches using biomaterials to encapsulate mitochondria for regenerative therapy, and employing organ-on-a-chip platforms to create stable mitochondrial transplants. One exciting direction is our work on developing a mitochondrial donor biobank, which holds promise for advancing translational and clinical applications of mitochondrial transplantation.

As Founder and Director of Mito2i, I work to create a collaborative environment that bridges these research themes, facilitating a holistic understanding of mitochondrial health and contributing meaningfully to patient care and scientific advancement.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
An open-minded approach to data interpretation, coupled with a readiness to learn from diverse perspectives, has been central to my work. I emphasize critical thinking and foster a collaborative environment where my team feels encouraged to bring fresh insights that often lead to breakthroughs.

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?
Absolutely. I am passionate about promoting inclusion and equity and encouraging the integration of diverse perspectives into scientific inquiry. Barriers tied to one's background, training location, or cultural heritage often limit one's voice in science. I advocate for an environment where critical thinking benefits from varied perspectives, fostering a more comprehensive understanding of complex issues. Through this approach, we can create a more inclusive, effective, and impactful scientific community.

What do you most enjoy in your capacity as an academic or research leader?
Teaching is a true passion of mine. I enjoy sharing knowledge and learning from brilliant colleagues and students who inspire me immensely.

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 cherish time with my family, whether playing board games, going for nature walks with our dog, or building lasting memories with my daughter. These moments provide a refreshing balance to my professional life and are a constant source of joy.

Part 2: Ana Cristina Andreazza – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
To live fully in the present and embrace every moment along the way.

What is your greatest fear?
Failure to positively impact the lives of those who depend on our research.

Which living person do you most admire?
My mom. She dedicated her life to public service, uplifting individuals from underprivileged backgrounds in southern Brazil with unwavering compassion and commitment.

What is your greatest extravagance?
Enjoying the occasional dinner at a Michelin-starred restaurant.

What are you most proud of?
My daughter—her growth and resilience inspire me daily.

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

Figure 2. Science in collaboration and joy. The Andreazza Lab cultivates a nurturing environment where collaboration and leadership flourish, often brightened by visits from Skater, our beloved lab mascot (center) – a four-year-old Keeshond/American Eskimo mix who reminds us to take restorative breaks in nature. Top right, then going clockwise: the Andreazza Lab team featuring (back row) Daniel, Jaeyoung Choi, Timofei Chernanga, Pavel Powlowski, David Bodenstein, Tiago S. Silva, Thisha Ravindran, (front row) Erika Beroncal, Lauren Pappis, Kassandra Zachos, Dana El Soufi-El-Sabbagh, Anna Gimenez, Angela Kwak, and special guests Skater and Isabela. Top right adjacent: connecting with courageous and brilliant minds, such as Thomas C. Zachos. Above bottom right: witnessing the field's growth, we collaborate with visionary leaders like Kirk Nylen and Franco Vaccarino at Metabolic Mind. Bottom right: my family's unwavering support and inspiration – Marles and, in loving memory, Armando Andreazza. Bottom left: having good times with Michael Berk in Crans-Montana, Switzerland. Above bottom left: with my beloved family, James and Isabela Pierlot. Middle left: MITO2i (Mitochondrial Innovation Initiative) represents our commitment to fostering innovation, as shown with Sonya Brijbassi. Top left: the joy of traveling, sharing knowledge, and building collaborations and friendships is evident in partnerships with esteemed colleagues such as Marion Leboyer, here on an e-scooter in the urban landscape.

What is your greatest regret?
I consciously try to live in the moment and learn from each experience.

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

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

What do you consider the most overrated virtue?
Listening—when it is done superficially without truly understanding or engaging with others.

What is your favorite occupation (or activity)?
Walking or hiking in nature.

Where would you most like to live?
Wherever my family is, that is my actual happy place.

What is your most treasured possession?
My family.

When and where were you happiest? And why were so happy then?
The day my daughter was born. It began an indescribable journey of joy, love, and growth.

What is your current state of mind?
Optimistic. I feel a sense of hope as mitochondrial research gains recognition as a critical factor in many diseases, bringing us closer to innovative therapies.

What is your most marked characteristic?
Passion. I am enthusiastic, expressive, and wholeheartedly committed when believing in a cause or helping someone in need.

Among your talents, which one(s) give(s) you a competitive edge?
My openness to listening to diverse viewpoints and synthesizing them into a cohesive understanding.

What do you consider your greatest achievement?
My family—their support and presence are invaluable to me.

If you could change one thing about yourself, what would it be?
I would ease my tendency to overthink.

What do you most value in your friends?
Their readiness to support when needed.

Who are your favorite writers?
My husband. His ability to synthesize knowledge and captivate his audience through his writing deeply inspires me.

Who are your heroes of fiction?
Monica is a Brazilian cartoon character—a fierce and passionate seven-year-old girl who always stands up for herself and others.

Who are your heroes in real life?
Mitochondria—these tiny structures are essential to life, driving energy and function in our cells.

What aphorism or motto best encapsulates your life philosophy?
Keep going; good things will happen.

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INNOVATORS & IDEAS: RESEARCH LEADER

Inga D. Neumann: Molecular underpinnings of the brain oxytocin system and its involvement in socio-emotional behaviour: More than a love story

Brain Medicine September 2025;1(5):17–20; doi: https://doi.org/10.61373/bm024k.0139

Keywords: Oxytocin, brain release, stress, anxiety, social fear, peripartum

Professor Inga Neumann stands at the forefront of neuropeptide research, bringing over three decades of expertise to her role as Chair of the Department of Behavioural and Molecular Neurobiology at the University of Regensburg, Germany. Her journey in science began in East Germany at the Karl-Marx-University in Leipzig (now the University of Leipzig), where she earned both her diploma in biology and her PhD. After the fall of the Berlin Wall, her career path led her through a postdoctoral position at the University of Calgary in Canada and seven enriching years at the Max-Planck Institute for Psychiatry in Munich before assuming her current position at Regensburg in 2001. As the first woman to be appointed full professor at the Faculty of Biology and Preclinical Medicine, she has shaped the University's neuroscience landscape by establishing and directing the Elite Masters Programme in Experimental and Clinical Neuroscience. Currently, she heads the Graduate School "Neurobiology of Socio-Emotional Dysfunctions," a prestigious program funded by the German Research Foundation since 2017. The heart of her research lies in understanding how neuropeptides, particularly oxytocin, vasopressin, and CRF, orchestrate stress responses and social behaviours. Her work spans multiple levels of analysis – from molecular mechanisms and epigenetics to neural circuits and behaviour – primarily using rodent models to unlock the mysteries of the social brain. In this Genomic Press Interview, Professor Neumann shares her reflections on a life dedicated to unravelling the intricate relationships between brain chemistry and behaviour, offering insights into both her scientific journey and personal philosophy.

Figure 1. Inga D. Neumann, PhD, University of Regensburg, Germany.

Part 1: Inga D. Neumann – 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 father, a physicist and mathematician working at the Carl Zeiss company in Jena, East Germany, kindled my interest in scientific phenomena, astronomy, physics, and genealogy. My parents also taught us critical and scientific thinking and how to appreciate nature. My early love for the beauty of nature arose along with my interest in horses, with the possibility of riding through the meadows and forests surrounding my Thuringian hometown. However, governmental restrictions in East Germany thwarted my original goal of becoming a veterinarian. Instead, I studied biology at the Karl Marx University in Leipzig, which has now returned to its original name of the University of Leipzig. At the Zoological Institute of that University, I became fascinated by the brain and ways of deciphering its secrets during my work for my diploma thesis in Rainer Landgraf's lab.

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

It has always been easy for me to develop ideas to take on leadership or responsibility in my private life and scientific environment. However, I had never seriously aimed to become a full professor at a university. Moreover, before being offered the position of Full Professor and Chair of the Department of Neurobiology and Animal Physiology at the University of Regensburg in 2001, I had never held the official group leader position. I only applied for the position because my contract at the Max-Planck-Institute was temporary, and my Heisenberg grant from the German Research Foundation (DFG) was limited to 5 years. Thus, I was thrown in at the deep end and suddenly led a group of elderly scientists and technicians working on cockroaches (*Blatta americana*) at the Institute of Zoology in Regensburg. I was the first woman employed as a full professor at the Faculty of Biology and Preclinical Medicine. I was the mother of 2 children, one of whom was just 3 years old, with the father working 120 km away from Regensburg and only returning home at weekends. This was where I started to oversee the substantial structural remodelling of more

Received: 11 December 2024. Accepted: 13 December 2024.
Published online: 24 December 2024.

than 30 rooms, old labs, and offices to enable my future research with rodents. I never considered attending a leadership or management course, nor did the University offer any such options at this time – you either succeeded or failed. But it was a fantastic time. I had complete freedom to shape the future research structures (limited only by financial restraints), to establish and build animal laboratories and behavioural facilities, to employ enthusiastic people, to think about how to hone my research profile, and, step by step, to successfully apply for research grants. Thus, there were no defining moments that channelled me towards that leadership responsibility; it was instead a continuous process during which I grew into the role.

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

As part of the research for my diploma thesis at the Karl-Marx-University in Leipzig, we aimed to monitor the release of the neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) in the rat brain during relevant physiological stimuli; e.g., suckling or osmotic stimulation. At the time, it was a fascinating hypothesis that, on the one hand, these neurohormones in the blood have distinct physiological functions, such as milk ejection or antidiuresis, and, on the other, are simultaneously released in the brain to promote respective behaviours. During our early research, we used push-pull perfusion techniques, and then later, during my PhD studies, we advanced to using microdialysis approaches. For more than 40 years, these intracerebral microperfusion techniques combined with extremely sensitive and specific radioimmunoassays for detecting the nonapeptides in the brain samples were the tools of choice to reveal the dynamics of neuropeptide release within distinct brain regions in the conscious and behaving animal. Thus, we monitored the release of OXT and AVP in the hypothalamic regions of origin or other limbic regions during physiological conditions, including suckling and birth, mating, exposure to various stressors, or social interactions. We also compared the intracerebral release patterns of these neuropeptides their secretion from the neurohypophysis into the blood and realized distinct differences in their secretory profile.

However, my beginnings as a scientist behind the "Iron Curtain" were bumpy. We had to build the concentric push-pull cannula systems, the U-shaped microdialysis probes, and perfusion pumps ourselves.[1] A dentist donated an old dental drill and dental cement. We did not have access to a stereotaxic frame. We had to use a divider, a ruler, and our stable hands to determine the stereotaxic coordinates and to keep the pull cannula in the correct position until the dental cement solidified. After Germany unified and experimental conditions had substantially improved, I continued to combine intracerebral microperfusions with many other methods to reveal the functional impact of OXT released within the brain. Realizing that the same molecule has distinct but synergistic functions in the periphery of the body (promotion of labor, milk ejection) and within the brain (maternal behaviour, stress buffer, anxiolysis) in the period of motherhood was a fascinating insight.

At the Max-Planck-Institute for Psychiatry in Munich, where I was offered a senior postdoc position, my scientific horizon was broadened substantially by integrating psychopathological aspects into my research. My fascination with brain neuropeptides, their intracerebral release patterns, and behavioural or physiological functions remained unbroken. So we started to focus on the potential role of the brain's OXT and AVP systems as therapeutic targets for psychiatric diseases such as depression and anxiety disorders or autism. These aspects remain the focus of my ongoing research using suitable animal models of chronic stress, depression- and anxiety-related behaviours, and social anxiety disorder. I was always motivated by the fact that the development of clinically relevant animal models is key to revealing the underlying mechanisms of specific symptoms of psychopathologies.

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

The large class of neuropeptides is a distinct group of neuromodulators that play a substantial role in all aspects of neuronal and glial functions and, thus, in all aspects of behaviour under healthy and pathological conditions. I am convinced that increasing our knowledge about the stimuli, dynamics, and consequences of their intracerebral release at the behavioural, physiological, cellular, and molecular levels will improve our understanding of general brain mechanisms. I hope that our studies revealing basic mechanisms of neuropeptide release, intraneuronal and intra-glial receptor-mediated signalling cascades, and their behavioural functions are helping to pave the way for interpreting the many and still growing number of human experiments targeting the OXT system. OXT can be applied intranasally in humans, and this treatment was shown to affect all different kinds of socio-emotional behaviour. Although there is still a long way to go to reveal transport into the brain, brain targets, suitable dosing, and treatment duration, the hope is that one day it will be possible to apply OXT reliably to treat – for example – treatment-resistant patients suffering from anxiety disorders, especially social anxiety, but also autism and schizophrenia.

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

To reveal underlying mechanisms of social fear, we are currently focusing on the role of brain OXT and CRF and other potential neuroactive molecules, such as non-coding RNA or endocannabinoids, in social anxiety (DOI: 10.1038/npp.2011.329). In this context, we have developed a reliable mouse model of social fear conditioning, an operant conditioning paradigm (DOI: 10.1038/s41583-023-00759-w). Here, we also include aspects of increased vulnerability to social fear after exposure to chronic psycho-social stress, early life stress, or, in contrast, of being resistant to social fear conditioning: for example, during lactation (DOI: 10.1016/j.cub.2018.02.044) or after mating (DOI: 10.1016/j.psyneuen.2024.107083), i.e., at times of highest activity of the brain OXT system.

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

As the responsible scientist behind many PhD and postdoctoral students' work, I feel obligated to win sufficient research funding to ensure their livelihoods and research for as many years as possible. THINK BIG is the word I often use to encourage innovative research without thinking of the financial limits in the first instance. The manuscripts we submit to any journal also reflect our work's quality. Thus, first (and last) authors have to earn these positions by producing the best manuscript draft possible, which I then revise thoroughly and repeatedly – up to 13 times, a time-consuming learning process for all persons involved.

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

I feel incredibly privileged always to work with the most talented, interested, and intelligent young people, with whom I can share my fascination with neuroscience in general and with the neurobiology of socio-emotional behaviour. Although, the development of their academic skills is a bumpy and energy- and time-demanding way, it is rewarding to see PhDs and postdocs grow in their role as future research leaders, starting with the supervision of student research assistants, Bachelor's and later Master's students, and continuing their careers in academia or industry.

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?

Here, I want to mention three aspects that are particularly important to me and help me to maintain a good work-life balance. The first is spending time with my family and, for the last 2 years, enjoying being a grandma for the first time. The second is the high-quality time I spend singing in various choirs and enjoying performances of classical pieces by Bach, Brahms, Mendelsohn, or Handel as a small individual being part of a large team.

[1] Neumann ID. Monitoring oxytocin signaling in the brain: More than a love story. Compr Psychoneuroendocrinol 2023 Sep 6;16:100206. doi: 10.1016/j.cpnec.2023.100206

Figure 2. Inga D. Neumann working at the Tacugama Chimpanzee Sanctuary in Sierra Leone, preparing enrichment material for chimpanzee orphans.

And – last but not least – I want to mention my passion for nature and preserving biodiversity. Hiking in the incredible Alps or in the nearby Bavarian Forest is a great way to exercise and gives me inner peace. At a very local level, I support environmentally friendly strategies as a municipal council member.

Further afield, I substantially support the Tacugama Chimpanzee Sanctuary in Sierra Leone, where I run a small scientific project on chimp orphans (see Figure 2). I also support their fantastic work in raising the environmental awareness of pupils and young adults or supporting the communities around the national parks, where wild chimpanzees are still found but endangered. In these villages, Tacugama supports their agricultural work and educates rangers. I plan to spend more time at Tacugama in the future.

Part 2: Inga D. Neumann – Selected questions from the Proust Questionnaire[2]

What is your idea of perfect happiness?
Lucius Annaeus Seneca said "true happiness is to enjoy the present without anxious dependence upon the future". I do not think there is perfect happiness, but we have moments of great happiness.

What is your greatest fear?
On a personal level, I fear losing my cognitive functions with aging. At a global level, I fear the further loss of our world's incredible biodiversity due to continuous and almost unchanged human activity, our careless use of available resources, and climate change.

Which living person do you most admire?
I deeply respect people who change their lifestyles and habits for environmental reasons. This can be their food choice, travel methods, altering consumption habits, or actively demanding appropriate political decisions.

What is your greatest extravagance?
To take a large jar of Nutella with me while traveling to and working at the Tacugama Chimpanzee Sanctuary in Sierra Leone, which significantly brightens my otherwise dry breakfast each morning (see Figure 2).

What are you most proud of?
To have successfully combined children and research at a time when this was not so usual in united Germany, when kindergartens and afternoon care in schools were not always available.

What is your greatest regret?
That I did not learn a musical instrument properly to a high standard as a child.

What is the quality you most admire in people?
Honesty, including acknowledging one's failures and weaknesses.

What is the trait you most dislike in people?
Selfishness and ignorance of the need to change our living habits to prevent further damage to nature and climate change caused by our species.

What do you consider the most overrated virtue?
Intelligence.

What is your favourite occupation (or activity)?
Listening to or performing classical music, discussing new research projects, but not answering questionnaires.

[2] 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.

Where would you most like to live?
In the Bavarian village close to the banks of the river Danube where I have lived for the past 24 years.

What is your most treasured possession?
The old genealogy tables showing the many different branches of my ancestral family tree going back to the 15th century, along with old letters and family photos.

When and where were you happiest? And why were you so happy then?
I remember exceptionally happy moments reading books to my children when they were very small and when they started talking, which are repeated from a different perspective with my grandchild now. I have happy and enthusiastic moments during a triumphant performance by our choir. I am also happy sitting in my garden, listening to and watching birds, wild bees, bumble bees, and dragonflies with a good cup of tea, and knowing I can repeat these moments anytime. Moreover, there were always truly delightful moments when we were awarded substantial research funding, for example, the funding for our Graduate School in 2017, and again in 2021 by the German Research Foundation.

What is your current state of mind?
I am among the many people who are deeply concerned about current worldwide political and ecological developments. It takes an immense amount of optimism to feel confident about a bright future for our grandchildren.

What is your most marked characteristic?
Optimism and determinism.

What do you consider your greatest achievement?
That I completed several half marathons, and that I was almost able to keep pace with the local rangers in the rainforest of the Loma National Park in Sierra Leone setting up camera traps for monitoring wild life.

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

What do you most value in your friends?
Being good partners to talk to in happy and sad moments, and humour.

Who are your favourite writers?
From Stefan Zweig to Ken Follett.

Who is your favourite hero of fiction?
Peter Pan.

Who are your heroes in real life?
I admire people who show civil courage or take real risks to protect civil rights or our environment.

What aphorism or motto best encapsulates your life philosophy?
"He or she who has a why to live can bear almost any how." (Friedrich Nietzsche – who was my great-great-grandmother's cousin).

Regensburg, Bavaria, Germany
9 December 2024

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INNOVATORS & IDEAS: RESEARCH LEADER

Michael C. Oldham: Clarifying the cellular and molecular architecture of the human brain in health and disease through gene coexpression analysis

Brain Medicine September 2025;1(5):21–25; doi: https://doi.org/10.61373/bm025k.0080

Keywords: Human brain transcriptome, gene coexpression analysis, glioma, human brain evolution, metascience

Michael C. Oldham, PhD, is a faculty member in the Department of Neurological Surgery and the Brain Tumor Center at the University of California, San Francisco (UCSF). Over the past twenty years, he has developed and applied novel computational and experimental strategies for studying the cellular and molecular heterogeneity of human brain samples in normal and pathological states. During his PhD with Dan Geschwind at UCLA, he performed the first genome-wide analysis of transcriptional covariation in the human brain, discovering highly reproducible patterns of gene activity corresponding to distinct cell types and states. After a brief postdoctoral stint with Steve Horvath at UCLA, he was unanimously selected as a UCSF Sandler Faculty Fellow, which provided him with R01-equivalent funding and principal investigator (PI) status in the new UCSF Broad Stem Cell Center. After completing his Sandler Fellowship, he was recruited to join the faculty of the Department of Neurological Surgery and the Brain Tumor Center at UCSF, where he applies the computational and experimental strategies he has developed to study malignant gliomas. At UCSF, he has served as the PI on multiple R01 grants focused on elucidating the cellular and molecular architecture of normal and pathological human brain samples. Dr. Oldham has also prioritized the creation of novel informatics resources that organize vast amounts of gene expression data and analysis results for the neuroscience research community. These efforts have convinced him of the need for new technology infrastructure to modernize scholarly communication around data analysis. In this Genomic Press Interview, Dr. Oldham is happy to share his unorthodox scientific and meta-scientific journey with our readers.

Part 1: Michael C. Oldham – Life and Career

Where were you born, and where do you live now?
I was born in New York City and I currently live in Corte Madera, California, USA.

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for Science?
I grew up in the suburbs of New York City in a family of physicians. My father, John M. Oldham, is a distinguished psychiatrist and past President of the American Psychiatric Association. My mother, Karen P. Oldham, was an internist at Columbia for many years, and her father, Bernard Pacella, was a distinguished psychiatrist and past President of the American Psychoanalytic Association. Other family members were also physicians and growing up, I assumed that medicine was also my path. However, that path was not to be.

Figure 1. Michael C. Oldham, PhD, University of California, San Francisco, USA.

I attended Duke University and graduated at the ripe age of 20 with a BS in Psychology and a pre-med focus. I had shadowed physicians, volunteered in the ER, taken the MCAT, and performed well. However, when it came time to apply to medical school, I could not bring myself to do so. It felt like something was missing, and I recognized it for what it was: I did not feel a strong, intrinsic desire to treat patients, and I knew that was a red flag. So, I stepped off the medical school conveyor belt with no Plan B.

I spent about six months traveling around Europe by myself after college, reflecting on what I might do instead, but mostly drawing blanks. When I returned to the States, I visited my best friend in San Francisco,

Received: 23 June 2025. Accepted: 25 June 2025.
Published online: 8 July 2025.

where he was trying to make it as a rock star. Although I had not spent much time in California, I instantly fell in love with the Bay Area and decided it was where my future lay. So, I packed up my 1989 Toyota Camry and drove across the country to start a new chapter in life.

I needed to get a job, and my friend connected me with his college buddy, who worked at an advertising agency called Goldberg Moser O'Neill, located on Maiden Lane, just off Union Square in downtown San Francisco. The next thing I knew, I was a Media Planner managing multimillion-dollar advertising budgets on behalf of large corporations, such as Dell Computer and Symantec. It was a fun job, filled with young people and social activities at a time when the Internet was just being born. After a couple of years, I took a new job doing similar work at a company called Organic, which was one of the first website design shops in San Francisco. The company went public, and I thought I might strike it rich, but the market collapsed before I could sell any shares.

I had never expected to work in advertising. Although I had fantastic supervisors, learned a great deal, and formed strong relationships, the work was deeply unsatisfying to me. My professional unhappiness prompted me to revisit my academic studies in search of that spark, that feeling that comes from trying to understand something that stirs you in a way you cannot quite explain. I had always been fascinated by the brain and by language – the beauty of words, the evolution of their meaning over time, and the miracle by which infants acquire them. I started reading books about language and its evolutionary origins. In particular, I spent a considerable amount of time reading *"The Symbolic Species"* by Terrence Deacon, which helped galvanize my interest in this topic. I realized that I wanted to study something that was *at the root*: something that was fundamental to the human experience. It occurred to me that the question of how human language came to exist was synonymous with another, more neuroscientific question: What makes a human brain different from a chimpanzee brain?

Humans and chimpanzees diverged about six million years ago. Although our genomes are more than 98% identical, something happened during that time frame that set *Homo sapiens*, the knowing human, on a radically different evolutionary path, giving us cognitive abilities that are qualitatively distinct from those of all other creatures that have lived. Essentially, the genetic changes that gave rise to the modern human brain were the catalyst for life as we know it. What could be more root than that? I felt that spark and knew that I wanted to study human brain evolution. It was around that time that I figured out I could study the brain without pursuing an MD, and I applied to several neuroscience PhD programs on the West Coast.

It was a tough sell. I had been out of college and Science for over five years, and my research experiences were relatively limited. However, I was laser-focused and filled with passion, and sometimes that goes a long way. Although most programs rejected me, UCLA gave me a chance. When I met Dan Geschwind, who shared my newfound interest in human brain evolution, I saw the path before me and joined his lab.

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

After joining Dan's lab, I began working at the bench, performing Northern blots to compare the abundance of specific mRNA transcripts between human and chimpanzee brain samples. The work was analog and laborious, yielding many ambiguous results. Fortuitously, the first microarray datasets produced from human and chimpanzee brain samples were published at around the same time by Svante Pääbo's group. Rather than studying one transcript at a time, here was an opportunity to study thousands in parallel. I desperately wanted to learn how to analyze these data, but I had no computational skills or programming experience. Luckily for me, Dan collaborated closely with Steve Horvath, a UCLA faculty member who had trained as a mathematician but crossed over into biostatistics. Today, Steve is probably most famous for his discovery of the epigenetic clock. However, at the time, he had just developed a methodology called "Weighted Gene Coexpression Network Analysis", or WGCNA. Unlike differential expression analysis, which seeks to compare the mean expression levels of individual genes between two or more cohorts, gene coexpression analysis seeks to identify the most robust patterns of gene activity in a biological system. Working with Dan and Steve, I learned the rationale behind WGCNA and how to program in R. Within a few months, I was using it to analyze the microarray data that had captured my attention.

This effort was fruitful, revealing patterns of gene activity that were conserved between human and chimpanzee brains, as well as others that were not. We published our study in *PNAS* (my first paper, 2006, DOI: 10.1073/pnas.0605938103), and I had the green light from Dan to graduate. However, I did not want to! After completing my first study, I began to apply WGCNA to other, larger gene expression datasets derived from human brain samples. This led to a 'eureka' moment when I realized that many of the recurrent patterns of gene activity I was seeing corresponded to transcriptional signatures of different neurobiological cell types. Upon reflection, it made perfect sense: variation in the cellular composition of bulk tissue samples should inevitably drive the covariation of markers for different cell types. This central insight formed the basis for my second paper, published in *Nature Neuroscience* (2008, DOI: 10.1038/nn.2207), which described these signatures and demonstrated how gene coexpression analysis of bulk tissue samples can reveal optimal markers of cell types and states. This insight still forms the central thesis for my lab today.

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?

For many years, I have been tracking the meta-scientific literature on research reproducibility with growing alarm. Nearly all studies that have systematically examined this topic have reached the same conclusions: most published findings are not reproducible, and even those that are often have effect sizes that are much smaller than initially reported. As I internalized these findings, I started to feel despair. After all, if most of the findings we toil to produce cannot feasibly be reproduced, what is the point? I spent a considerable amount of time thinking about this. Like many seemingly intractable problems, a glimmer of a partial solution began to emerge when I broke the problem down into smaller pieces.

Although the reproducibility crisis has many causes, there is no reason in principle that data analysis, which is increasingly central to biomedical research, should not be completely reproducible. However, it often is not. In practice, data and code may be unavailable or only partially available if journal editors do not enforce this stipulation. Methods sections may omit critical experimental or analytical details and descriptions of data or metadata may not align between journal articles and data repositories. Resolving these challenges often requires timely feedback from the original authors, which can be uneven at best. These realities highlight important shortcomings in our system of scholarly communication and suggest a need for reform.

Motivated by these concerns, I joined a standing UCSF Academic Senate Committee on Library and Scholarly Communication. Now, as Vice Chair of that committee, I have launched a pan-UCSF Academic Senate Task Force on research data and metadata standardization, which I currently chair. The purpose of this Task Force is to define community standards for the packaging and description of data and metadata by UCSF investigators. Although this topic may sound dry, these standards are an essential prerequisite for more open and reproducible Science, more precise forms of biomedical knowledge representation, and more efficient forms of collaboration, teaching, and scholarly communication.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

I chose not to finish my PhD at the earliest opportunity (i.e., after my first major publication). Some people (possibly including Dan) thought this was a bit nuts. Instead, I spent two more years in the lab and produced a second publication that had an even greater impact. As a result of this choice, I was unanimously selected as a UCSF Sandler Faculty Fellow, which provided me with the independence and funding to establish my own lab almost immediately after graduating from graduate school.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
I did not have a full postdoctoral experience, as I was awarded the Sandler Fellowship only a few months into my postdoctoral work with Steve Horvath. However, the main habit I started with Dan and Steve, integrating patterns of gene activity across many independent datasets, remains the backbone of my lab's work today, as this practice increases statistical power and builds confidence in our findings.

Please tell us more about your current scholarly focal points within your chosen field of Science.
I was recruited by the Department of Neurological Surgery and the Brain Tumor Center at UCSF to apply my approach to adult malignant gliomas, which are notoriously heterogeneous and aggressive. It has been a fascinating transition into cancer biology, and I am grateful to have cultivated a unique perspective on gene activity in the human brain from my prior work. We have analyzed, integrated, and compared patterns of gene activity from vast amounts of neurotypical human brain samples and malignant gliomas. These efforts have focused our attention on vascular cells, which are difficult to isolate and capture for single-cell analyses. By comparing the vascular patterns of gene activity between normal human brains and gliomas, we have identified high-confidence molecular markers of glioma vasculature. Many of these genes encode cell-surface proteins that provide molecular 'zip codes' for gliomas that are accessible via the bloodstream. We are now advancing these targets in various translational directions, including for use as biomarkers and the development of novel therapeutic agents.

Of course, the information captured by coexpression analysis of human brain samples goes far beyond the vasculature. To organize and disseminate our findings, we have developed the OMICON platform (theomicon.ucsf.edu) to promote FAIR (**F**indable, **A**ccessible, **I**nteroperable, **R**eusable) research practices involving human brain gene coexpression networks. Currently, OMICON contains structured gene expression data for >17K bulk human brain samples (~10K normal and ~7K malignant glioma), which were collected from diverse public repositories and consortia. Using these data, we have identified ~100K gene coexpression modules, which have been extensively characterized via enrichment analysis with thousands of curated gene sets. All datasets, metadata, gene coexpression networks, enrichment results, and analysis steps can be browsed with an interactive workflow visualization tool, which promotes accessibility, reusability, and reproducibility by maintaining complete data provenance with unique identifiers. To promote findability, we have developed an advanced search engine that identifies datasets, samples, modules, and more by filtering standardized metadata. Through this functionality, OMICON aims to foster community and concentrate therapeutic efforts on reproducible analyses of transcriptional variation in the normal human brain and brain tumors.

What impact do you hope to achieve in your field by focusing on specific research topics?
Glioblastoma is a terrible disease. Despite the best efforts of a generation, we have not made significant progress in terms of patient care and outcomes. I hope our efforts can contribute to better outcomes for these patients. In a more general sense, I aim to develop new technology infrastructure to enhance the efficiency of biomedical research by enabling faster and more accurate data discovery, ensuring bioinformatic reproducibility, and fostering new forms of collaboration, teaching, and scholarly communication centered on data analysis.

What do you most enjoy in your capacity as an academic or research leader?
The thrill of discovery never gets old! But I am also blessed to work with talented people from all over the world who seek only to pierce the veil. It is a true source of joy to work closely with young people who are not only smart but also filled with curiosity, passion, and grit.

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 you feel strongly devoted to?
We need to reimagine scholarly communication for the 21st century. For centuries, scientists have communicated their findings through long-form narrative journal articles. This is not how most kids today are trained to consume information, and I fear we will lose a generation of young scientists as a result. Furthermore, the reproducibility crisis is a canary in the coal mine. If that does not warrant transformative scrutiny, what will?

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 am fortunate to live in Marin County, Northern California, where you are never more than five minutes from a trailhead. You will often find me walking alone in the woods, lost in thought. I am also fortunate to have a large group of dear friends from my early SF days who practice a consistent motto: ABC (always be celebrating!).

Part 2: Michael C. Oldham – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
I am determined, which helps me execute long-term plans effectively.

Among your talents, which one(s) give(s) you a competitive edge?
I like to think I have a lot of mental stamina. I can focus on a task for an extended period (even if I don't like it), and I don't give up on a problem until I have exhausted all possible approaches to solving it. I am also good at tuning things out (a trait I inherited from my mom!).

If you could change one thing about yourself, what would it be?
I wish I were more of an extrovert. I can turn it on when I need to, but it's not my natural state.

What is your current state of mind?
Tired! I am writing this at the International Conference on Brain Tumor Research and Therapy (ICBTRT) meeting in Japan, and my body is not sure what time it is.

What is your idea of perfect happiness?
The absence of stress and the presence of love.

When and where were you happiest? And why were you so happy then?
I subscribe to different flavors of happiness. There is happiness with friends, which tends to peak each year in the ephemeral and inestimable

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

Figure 2. Mike Oldham, in celebration mode.

magic of Black Rock City. There is also happiness with my family, which grows each year alongside my wife, Gwen, and our son, Evan. However, I would like to think that the happiest moments are yet to come.

What is your greatest fear?
Failure – especially if that results in being eaten by a giant spider.

What is your greatest regret?
I regret not having more self-confidence when I was young – but better late than never!

What are you most proud of?
The life I have created in the Bay Area, including my amazing wife, Gwen, our preternatural son, Evan, our lakeside home, and my faculty position in one of the world's greatest departments and research universities.

What do you consider your greatest achievement?
Scientifically, we have proposed a statistically motivated solution to one of the core problems in biomedical research: how to identify optimal molecular markers for cell types and cell states. I am very proud of this solution, which involves integrating patterns of gene activity corresponding to cell types or states across vast amounts of bulk data representing many billions of cells. Therefore, the results are highly robust and reproducible. But in life, nothing compares to raising a child.

What or who is your greatest passion?
I am a connoisseur of electronic music which I have listed to almost exclusively for the past 25 years.

What is your favorite occupation (or activity)?
My friends include many dancers and DJs (including me), and we gather regularly to dance and celebrate in beautiful spots around San Francisco and Northern California (see Figure 2).

What is your greatest extravagance?
I spend thousands of dollars a year on a new B3 vitamin and NAD^+ precursor called nicotinamide riboside. I discovered it while monitoring the scientific literature and came across a *Science* article (2016, DOI: 10.1126/science.aaf2693) showing that it extended the lifespan of aged mice. It turned out that this was based on previous work showing that nicotinamide riboside promoted Sir2 silencing and extended lifespan in yeast; Belenky P et al., Cell, 2007, DOI: 10.1016/j.cell.2007.03.024. Nicotinamide riboside has since demonstrated efficacy in treating diverse conditions across various model organisms and is currently in clinical trials for multiple indications—see: Berven et al., *Nat Commun* 2023, DOI: 10.1038/s41467-023-43514-6; McDermott MM et al. *Nat Commun* 2024, DOI: 10.1038/s41467-024-49092-5; Norheim KL et al., *Nat Aging* 2024, DOI: 10.1038/s43587-024-00758-1, and Shoji M et al., *Aging Cell* 2025, DOI: 10.1111/acel.70093. The topic of cellular aging and the role of NAD^+ in this process is fascinating.

What is your most treasured possession?
I am not a big consumer, but I do love my DJ controller. However, I do not treasure it as much as old photos of my friends and family.

Where would you most like to live?
Marin County, California! It is like the shire.

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

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

What do you consider the most overrated virtue?
Piety.

What do you most value in your friends?
Loyalty.

Which living person do you most admire?
My dad! I do not think I have known anyone with more integrity.[2]

Who are your heroes in real life?
My family members each in their own way. Jane Goodall. And anyone who consistently practices kindness.

If you could have dinner with any historical figure, who would it be and why?
He may not be a historical figure to most, but I would choose Larry Harvey. He saw things in people and cultures that others did not, and his efforts have touched the lives of millions around the world in ways that are truly unparalleled and comparable to no one else I can think of.

Who are your favorite writers?
The sad truth is that after devouring novels for most of my young life, when I became a scientist, my reading diet shifted almost exclusively to science-related articles and news. But if I had to draw from the past, I might choose Emily Dickinson, Vladimir Nabokov, and Gabriel Garcia Marquez.

Who are your heroes of fiction?
Don Quixote and Frodo Baggins.

What aphorism or motto best encapsulates your life philosophy?
Nothing in life is to be feared; it is only to be understood. – Marie Curie.

Tōyako, Hokkaido, Japan
23 June 2025

[2]The interviewee's father, Dr. John M. Oldham, is also featured in a companion Genomic Press Interview in *Brain Medicine*, 2025 — DOI: 10.61373/bm025k.0059.

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Funding Sources

This work was supported by the University of California, San Francisco, Program for Breakthrough Biomedical Research, NIH R01CA244621, NIH R01MH113896, NIH R01MH123156, and NIH R01CA292649.

Author Disclosures

Dr. Michael Oldham disclosed that after he started taking nicotinamide riboside, he invested in shares of one of the companies that manufactures it.

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INNOVATORS & IDEAS: ACADEMIC LEADER

John M. Oldham: Personality styles and personality disorders, a dimensional framework

Brain Medicine September 2025;1(5):26–29; doi: https://doi.org/10.61373/bm025k.0059

Keywords: Personality, personality disorders, leadership, education, psychiatry

John M. Oldham, MD, MS, stands as one of psychiatry's most influential architects of personality disorder theory and classification, a field he has indelibly shaped through decades of scholarship, clinical leadership, and systems-level innovation. He was born in Muskogee, Oklahoma, where family roots in frontier medicine instilled an early appreciation for human complexity, set the stage for a career spanning some of the most prestigious institutions in academic medicine, including Columbia University, Cornell Medical Center, the Medical University of South Carolina, and Baylor College of Medicine, where he held the Barbara and Corbin J. Robertson, Jr. Endowed Chair for Personality Disorders. In this in-depth Genomic Press profile, Dr. Oldham, former President of both the American Psychiatric Association and the International Society for the Study of Personality Disorders, traces his clinical evolution and reflects on leadership strategies that work in high-stakes psychiatric environments. He has published extensively across both clinical and conceptual literatures, with over 200 articles and books to his name, and is widely recognized for creating the New Personality Self Portrait, an assessment tool that bridges psychometric rigor with real-world clinical relevance. His role in developing the Alternative DSM-5 Model for Personality Disorders marked a profound epistemological shift—from rigid diagnostic categories to a dimensional system that more accurately reflects the gradations and interplay of personality traits. As editor for the *Journal of Psychiatric Practice*, *Journal of Personality Disorders*, and *Borderline Personality Disorder and Emotion Dysregulation*, he has also curated the evolving scientific discourse, foregrounding pragmatic, evidence-informed approaches to complex psychopathology. Perhaps most striking is his tenure as Chief Medical Officer for the New York State Office of Mental Health in the immediate aftermath of the 11 September 2001 (9/11) attacks, where he navigated public trauma, institutional pressure, and emergent psychiatric needs with clarity and resolve. Dr. Oldham's legacy endures in diagnostic paradigms and policy blueprints, and his rare capacity to integrate intellectual rigor with ethical depth—a hallmark of medical leadership at its highest level.

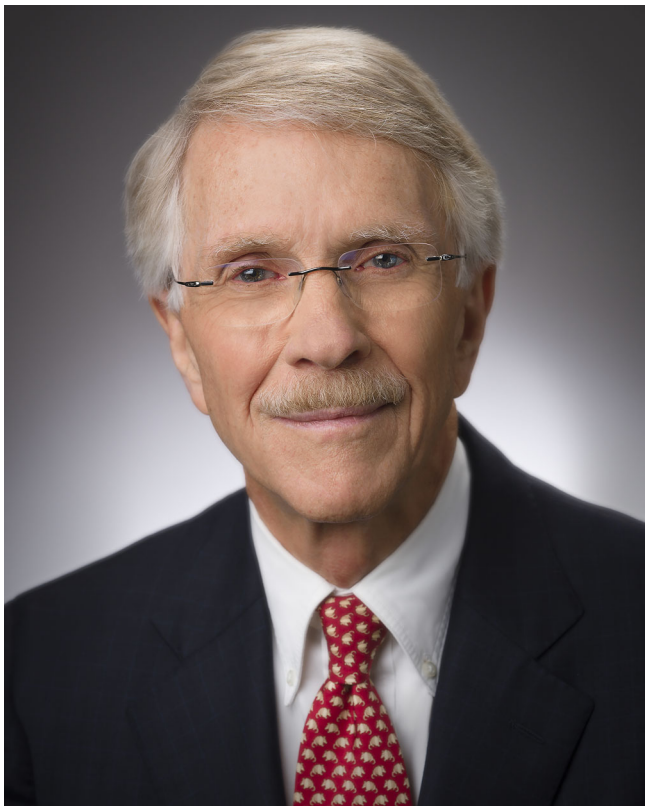

Figure 1. John M. Oldham, MD, MS, Baylor College of Medicine, USA.

Part 1: John M. Oldham – Life and Career

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

Medicine has played a big part in my family. I was born in Muskogee, Oklahoma, where my grandfather, Dr. I. B. Oldham, was one of the few pioneering town doctors at the turn of the century. Framed on my wall is his "License to Practice Medicine and Surgery in the Creek Nation," issued on 4 November 1903, before Oklahoma became a state, by the Creek Board of Medical Examiners. My uncle, Dr. I. B., Jr, followed in my grandfather's footsteps, and many years later, he was the presiding physician in the delivery room when my identical twin brother, James, and I were born. And many years later, our older brother, Newland, became a physician, with specialty training in cardiothoracic surgery at Baylor and Johns Hopkins, followed by a distinguished academic career as a professor of surgery at Duke.

So, the family legacy of medicine always beckoned, but it took me some time to get there. My father was an engineer in the oil and gas industry, and we lived in New Mexico and then Texas. High school was in Lubbock, Texas, from which my brother and I drove our 1955 Rocket-88 Oldsmobile cross-country to college at Duke. Neither of us had figured out a major, so we followed our father's advice and majored in civil engineering. Although we graduated from Duke as civil engineers, we realized engineering was not for us. James headed to Stanford Law School, eventually relocating

Received: 30 April 2025. Accepted: 7 May 2025.
Published online: 10 June 2025.

to Washington, DC, to become a professor at Georgetown Law School. He was later named the St. Thomas More Professor of Law and Legal History.

However, the siren call of medicine prevailed for me, and I entered medical school at Baylor College of Medicine in Houston. There, I opted for a double degree 5-year MD/MS program, earning a Master's degree in neuroendocrinology and an MD. In those years, what became clear to me was that I wanted to know more about human behavior and what makes us who we are. My Master's work was helpful, cementing a lifelong interest in research but helping me recognize that I was not cut out for a full-time research career. Psychiatry became the specialty for me, and I landed a wonderful psychiatry residency at Columbia and the New York State Psychiatric Institute (NYSPI), which turned out to be a professional home for a big chunk of my career. My final year of residency was special in many ways. That is when I met my future wife, Karen Pacella, MD, who became Karen Oldham, MD, in April of that year (1971). I was chosen to be Chief Resident, and working with my Chair, Larry Kolb, and Vice-Chair, Shervert Frazier, was truly a privilege–I learned a lot about leadership from them. I also began my psychoanalytic training at Columbia during that last year of residency.

Those were the days when the Vietnam War was winding down. I had been fortunate to enroll in the Berry Plan, which allowed me to complete my specialty training before assuming active duty. I served two years as a Major in the US Air Force, stationed at Andrews in Washington, DC. Now, as a Vietnam Era Veteran, I look back at my time in the USAF as one of those experiences you might never have chosen, but that are unique and valuable. Part of my job was to interview returning POWs who had been in solitary confinement for up to 7 years. They were sturdy heroes who seemed in remarkably good shape, but their mental health needs surfaced years later.

Karen and I returned to New York, and only a few months later, our first child, Madeleine, was born. Karen had completed training in internal medicine and became a staff physician at the Columbia Student Health Service. I joined the Columbia faculty, resumed my psychoanalytic training, started a part-time private practice, and began a salaried position in emergency psychiatry at Columbia-affiliated Roosevelt Hospital–well before the NY West Side had become gentrified, so that was trial-by-fire learning! Later, I was fortunate to become the residency training director at Roosevelt. By then, what began to emerge was one of the themes of my career. I have always been interested in psychodynamic thinking. But I wanted to apply those principles not just to the worried well, but to those with seriously disabling mental illnesses. And I wanted to be in an academic department to be able to teach and learn, while still finding time for my family (our second child, Michael, had joined us by then)–a challenging agenda!

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

I had a lucky break: one of my supervisors in psychoanalytic training was Otto Kernberg, who taught me about borderline personality disorder. At the time, Kernberg was the Medical Director of New York Hospital-Cornell Medical Center, Westchester Division, and when I finished my training, he offered me a job at the hospital, a 320-bed facility known for its intensive inpatient treatment. It all started to fit together, and an enduring central focus of my career emerged: to understand, treat, and teach about severe personality disorders. While serving as chief of an inpatient unit, I was invited to join a clinical research team led by Armand Loranger, and we developed one of the first semi-structured clinical research interviews to diagnose DSM-III-defined personality disorders, the Personality Disorders Examination (PDE).

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 seven richly rewarding years at Cornell, I was recruited by Herb Pardes to return to the Columbia faculty as Deputy Director of the New York State Psychiatric Institute (NYSPI), the oldest mental health research facility in the US, located on the grounds of the Columbia University Health Sciences campus. This was an excellent opportunity for my 44-year-old self, one that launched over 2 decades of amazing collaboration with world-class clinicians, educators, and scholars. NYSPI served as the home of the Columbia Psychiatry Department, and the NY state-funded core support for research was invaluable. I became Director of the Institute when Herb became Dean at Columbia. For a very long time, NYSPI received the highest level of (US) National Institutes of Health/National Institute of Mental Health (NIMH) research funding of any academic center in the country, and its research engine was in overdrive, with the likes of Nobel laureate Eric Kandel and foremost academic leaders such as Myrna Weissman, David Shaffer, Donald Klein, Sandy Glassman, Tim Walsh, Mike Liebowitz, to name a few. Along the way, I was fortunate to be appointed the Elizabeth K Dollard Professor of Clinical Psychiatry, Medicine, and Law at Columbia (an ironic alignment with my twin brother, the law professor at Georgetown).

Figure 2. A few days after 9/11, several New York state officials in hard hats at Ground Zero, which was still smoldering, as a reminder of the staggering challenges that were being faced–John Oldham, then Chief Medical Officer, NY State Office of Mental Health, is on the right, with his jacket over his shoulder.

Among many academic adventures, a group of us at NYSPI created a Unit for Personality Studies (UPS) led by Andy Skodol, who became Principal Investigator (PI), and I served as co-PI for the NY site of a major multi-year NIMH grant. That ambitious research program, led by John Gunderson at Harvard, was called the Collaborative Longitudinal Personality Disorders Study (CLPS), and it generated important findings about PDs for over a decade.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

A few years after I returned to NYSPI, New York State appointed its first-ever non-MD Commissioner of Mental Health (Richard Surles, PhD). He created a new position, Chief Medical Officer, to be his medical deputy, and he asked me to briefly serve in that capacity, part-time, while he recruited a full-time CMO. I had never imagined being in a leadership role in a state hospital system–at the time, the NY State Office of Mental Health (OMH) operated about 25,000 inpatient beds—and I was hesitant. But it turned out to be a remarkable opportunity. The Commissioner decided to keep me on, and I continued in that capacity from 1988 until I left New York in 2002 (see Fig. 2).

Space does not allow me to describe all of the things I learned in that big public bureaucracy, responsible for the welfare of the most in need and disabled in our field. But I will single out two things, as follows:

First, we created an annual multi-day OMH Research Conference in Albany, accessing state funds to bring clinicians from all state hospitals to interact with leading researchers and learn from them. The conference "broke the ice" between the researchers and the state hospital clinicians

and was held for over a decade, fostering educational and clinical research collaborations.

Second, the terrorist attack on the World Trade Center shocked the world. It did not turn out to be the expected medical/surgical disaster, as there were too few survivors. Instead, it was an emotional and psychological disaster, and the NY State Office of Mental Health had the lead responsibility to help the city and the state recover. As the senior physician in the agency, I was called upon to play a central role. I keep a photo, taken a few days after 11 September 2001 (9/11) of several of us in hard hats at Ground Zero, which was still smoldering, as a reminder of the staggering challenges that faced us all (see Fig. 2).

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

My family values have always made me conscientious and a good team player. The best leader is the leader who listens. Professional colleagues have described me as steady, calm, trustworthy, respectful, and flexible yet firm. I am even-keeled, but I can rise to the occasion when needed.

Please tell us more about your most relevant focal points – past or present – within your chosen field of science.

Personality Disorders

My good fortune in focusing on personality disorders led to many opportunities. For the American Psychiatric Association (APA), I chaired the first Practice Guideline (PG) for treating patients with BPD, published in the American Journal of Psychiatry in 2001. I have participated in a new edition of the BPD PG, which was just recently published. I was active in the International Society for the Study of Personality Disorders (ISSPD), serving as its President for four years and getting to know colleagues with similar interests throughout the world.

And there is another standout tale: Early in my career, I became concerned about the stigma surrounding personality pathology notions. By good fortune, I met a talented journalist, Lois Morris, and we devised a plan to write a book for the general public, to provide education about personality styles and disorders. The Personality Self-Portrait was published in 1990, followed by a revised version in 1995; it has been continuously in print for 35 years. Later, joined by Alok Madan, PhD, we developed an online version of the self-assessment test and text material, npsp25.com, which is a resource utilized worldwide.

Finally, I co-chaired the APA Workgroup on Personality and Personality Disorders, chaired by Andy Skodol, for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Steering Committee. We developed the Alternative DSM-5 Model for Personality Disorders (AMPD) in Section III of the DSM-5. Several of us published a Structured Clinical Interview for DSM (SCID) focused on the AMPD, SCID-AMPD, that is being used to study the model. I recently participated in a new DSM Steering Committee Workgroup that has recommended an updated version of this dimensional system for a future revision of the DSM.

Leadership

I have been privileged to serve in many leadership capacities. After years at Columbia, NYSPI, and OMH, I was recruited to become Chairman of the Department of Psychiatry at the Medical University of South Carolina in Charleston. Being in the deep South was a change of pace–we lived in a home built in 1850! MUSC is a fine academic center, and the psychiatry department was the one with the largest federal research support on campus. But it needed stabilized leadership, which the strong faculty teamed up with me to accomplish.

After 5 years in Charleston, I was recruited to return to my alma mater, Baylor College of Medicine, to serve as Executive Vice Chair of the psychiatry department and Chief of Staff at the Menninger Clinic. Menninger is the department's private teaching hospital, having relocated to Houston from its illustrious early years in Topeka, Kansas. Menninger was well-known to me, and at Baylor, it provided intermediate length-of-stay intensive inpatient treatment for patients with complex illnesses, often including severe personality disorders. We were able to organize a clinical research program to study our treatment strategies, leading to multiple publications about the work. During these years, I was asked to become a candidate for the position of President of the APA. With the strong support of my chairman and of the Menninger CEO, I agreed to do so and had the good luck to prevail. My years as President-Elect and President were formidably busy, but the experience was a highlight of my career. During those years, Menninger moved into a sparkling new facility and celebrated with a symposium featuring Tom Insel, then Director of NIMH, as well as Patrick Kennedy and many others.

What were the key impact areas of your research topics?

The key impact areas of my research and clinical interests are the many accomplishments described above and below, which have clarified, strengthened, and helped us advance our understanding of severe personality disorders.

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

I have been a lucky traveler in the world of academic medicine. I could not single out one role over others; they have all been immensely rewarding. Currently, I serve as editor or co-editor for three journals, which keeps me on my toes.

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 you feel strongly devoted to?

We are all citizens of our country in a changing world. We must be ambassadors for honesty, scientific integrity, fairness, compassion, and respect for our colleagues and citizens of all stripes.

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 been a long-distance runner for much of my life, having run the New York City Marathon three times. When I run or go for walks, I listen to recorded books, either historical fiction or good murder mysteries. I also love grand opera, having enjoyed the Metropolitan Opera in New York for many years and now the Houston Grand Opera.

Part 2: John M. Oldham – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?

Staying calm in stormy times and keeping my balance at all times.

Among your talents, which one(s) give(s) you a competitive edge?

Some who know me have said: "Don't be fooled, he has an iron hand in the velvet glove."

[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.

If you could change one thing about yourself, what would it be?
Outside of socializing at professional meetings, I am reserved. However, I would not mind being a little more gregarious, and I would like to be fluent in multiple languages.

What is your current state of mind?
I am generally pretty happy and satisfied.

What is your idea of perfect happiness?
I do not believe there is such a thing. However, keeping your glass at least half-full works best to make the most of what life brings along.

When and where were you happiest? And why were so happy then?
When Karen and I were married in New York and when our children were born. Needs no explanation.

What is your greatest fear?
The reality of the presence of corrupt cult leaders to exert power, cruelty, and callous destruction over the lives of millions.

What is your greatest regret?
I did not handle my work/life balance well enough, overloading myself with my career and limiting my social life to my nuclear family and my career friends. But I do not lament this too much; I have had a good run.

What are you most proud of?
Our children. Madeleine's career has been in the theater world as a dramaturg and sound designer, and she is a great ice hockey referee. Mike is a neuroscientist with his own lab at UCSF; he is PI on multiple NIH R01 grants, and his most recent R01 from the National Cancer Institute received a priority score in the 1st percentile.[2]

What do you consider your greatest achievement?
It is hard to say, but drive over the George Washington Bridge into Manhattan, and on your right, you will see a glass-clad modern building near the Hudson River. It is NYSPI's newest building, and the story of the land acquisition on which it was built (formerly called "Dead Dog Park") and the challenges to get it built is a long one. As NYSPI Director at the time, I was in the hot seat, but we got it done.

What or who is your greatest passion?
Music. Grand Opera, yes, plus the great romantics—Brahms, Rachmaninoff, Tchaikovsky, Chopin, and the like. I really appreciate classical fine art, particularly the Dutch old masters.

What is your favorite occupation (or activity)?
My profession as a psychiatrist, still trying to understand human behavior.

What is your greatest extravagance?
Recently, we took our 2 children, their spouses, and our grandson on an all-expenses-paid spring break trip to my old haunts: Cloudcroft, New Mexico (9,000 ft elevation), the White Sands, Santa Fe, and the Grand Canyon. It was worth every penny.

What is your most treasured possession?
The log house we built in the woods in upstate New York.

Where would you most like to live?
Where I now live, in Houston.

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

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

What do you consider the most overrated virtue?
"If you can't say anything nice, don't say anything at all."

What do you most value in your friends?
Friendliness.

Which living person do you most admire?
Otto Kernberg.

Who are your heroes in real life?
Champions of mental health—too many to list.

If you could have dinner with any historical figure, who would it be and why?
This would be a long list, but I will pick one: the German composer Richard Strauss. His music is unique (Der Rosenkavalier, Four Last Songs, and many more). I would like to hear how he captured pathos and intensity in his music, even in light-hearted works, and how that related to the turbulence in his country in the late 1930s and early 1940s.

Who are your favorite writers?
Charles Dickens, Lewis Carroll, Gabriel Garcia Marquez, Lawrence Wright, Erik Larson, Ken Follett, Greg Iles, and John Grisham.

Who are your heroes of fiction?
Ebenezer Scrooge, The Artful Dodger, Uriah Heep, Miss Havisham, Alice in Wonderland, The Cheshire Cat, and The Caterpillar.

What aphorism or motto best encapsulates your life philosophy?
Do unto others as you would have them do unto you.

Houston, Texas, USA
27 April 2025

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INNOVATORS & IDEAS: ACADEMIC LEADER

Siegfried Kasper: The importance of back-translation of clinical findings to basic science

Brain Medicine September 2025;1(5):30–33; doi: https://doi.org/10.61373/bm025k.0104

Keywords: Depression, treatment-resistant depression, anxiety, schizophrenia, brain imaging, neuropsychopharmacology

Professor Siegfried Kasper, a transformative pioneer in modern psychiatry, serves as Professor Emeritus at the Medical University of Vienna's prestigious Center for Brain Research, where his groundbreaking research continues to revolutionize the understanding of treatment-resistant depression's molecular basis. Following his distinguished tenure as Chair of the Department of General Psychiatry and later Psychiatry and Psychotherapy at the Medical University of Vienna from 1993 to 2019, Professor Kasper has authored over 800 peer-reviewed publications with an exceptional H-index of 131, establishing him as Austria's most frequently cited psychiatrist. His pioneering contributions have focused on demonstrating that psychiatric disorders have a biological basis alongside psychosocial determinants, exploring neuroendocrinological pathways as windows to the brain, and utilizing advanced imaging technologies, including CT, MRT, and PET, to study structural and functional changes in schizophrenia and depression. Professor Kasper was instrumental in introducing revolutionary psychopharmacological treatments, including SSRIs, atypical antipsychotics, and, most recently, intranasal esketamine, demonstrating their effectiveness in specific disease subgroups with improved side effect profiles. As founding president of the Austrian Society of Neuropsychopharmacology and Biological Psychiatry and former President of both the World Federation of Societies of Biological Psychiatry and the International College of Neuropsychopharmacology, he has shaped global psychiatric practice through his leadership of the European Group for the Study of Resistant Depression. His extraordinary achievements have earned him the Grand Decoration of Honor in Silver for Services to the Republic of Austria, the Austrian Cross of Honor for Science and Art First Class, the 2019 City of Vienna Award for Medical Science, the 2024 WFSBP Lifetime Achievement Award, and the 2025 CINP Pioneer Award. In this exclusive Genomic Press Interview, Professor Kasper shares profound insights from his remarkable career dedicated to transforming psychiatric treatment and improving countless lives worldwide.

Part 1: YOUR NAME – Life and Career

Where were you born, and where do you live now?

I was born in Salzburg, Austria, and live right now in Klosterneuburg a suburb of Vienna in Austria.

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

As a medical student, I developed a particular interest in brain anatomy. With great enthusiasm, I dissected the limbic system, wondering how emotions and thoughts are transported and modified through this system.

Figure 1. Siegfried Kasper, MD, Professor Emeritus, Medical University of Vienna, Austria.

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

During my specialization, which was at the Central Institute of Mental Health in Manheim Germany, which was in these days, one of the most advanced psychiatric university hospitals in Europe, conducting studies in epidemiology as well as biological mechanisms I was inspired by animal research from Michel Jouvet/France, who noticed that when he lesioned the raphe nuclei in cats they could not sleep anymore. I realized that this is precisely what I do see in my patients: they cannot sleep. Therefore, I started research on the serotonergic system in depression. However, my mentors alerted me that this could be the early ending of my scientific career, since research in depression was in firm hands in those days, with the norepinephrine theory of depression.

Received: 23 August 2025. Accepted: 26 August 2025.
Published online: 2 September 2025.

I was fortunate to have one of my first mentors, Helmut Beckman, return from the National Institute of Mental Health (NIMH), and he invited distinguished researchers like Bob Post and Dennis Murphy from the NIMH to visit us in Mannheim. The communications with these colleagues inspired me to join NIMH for further research.

During my research at the Clinical Psychobiology Branch at NIMH, I studied circadian rhythms and the influence of light therapy in seasonal affective disorders (SAD) with Tom Wehr. I conducted the first epidemiological study with Norman Rosenthal on seasonal variations of mood and behavior depending on the latitude the person lived and could demonstrate that further north in the US, higher rates of SAD and its subsyndromal form, a syndrome which I first described, can be found. Japanese colleagues replicated this finding. In addition to changes in mood and behavior, hormonal as well as immunological alterations can be detected with the turn of the seasons.

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 was privileged to work in a scientific environment with Heinz Häfner in Mannheim, as well as with Helmut Beckman, who clearly indicated to me that the diseases and, respectively, the symptomatology in our patients have specific mechanisms that await discovery from different angles. In those days, there was an enthusiasm for research in biological mechanisms in Germany, spearheaded also by Hanns Hippius from the Department of Psychiatry in Munich, who visited us several times in Mannheim. He once spoke to me with a confident smile, assuring me that I would have a great future in the field. I still remember these inspiring words very well and continued to use them later in my career when I mentored younger colleagues.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

When I started psychiatric training, I thought that psychoanalysis is the way to understand the psyche of our patients better. However, I soon realized that with this approach, I cannot help my patients to get out of the disease, and I was lucky enough to be trained by a psychoanalyst who was a professor of child psychiatry in Heidelberg, who performed genetic studies in so-called "neuroses". He made it clear to me that there are different approaches to understanding the psyche, and psychoanalysis is one way that needs to be connected with profound psychiatric and biological knowledge of the central nervous system. I do not think it was a mistake to perform a complete psychoanalytic training, laying over six years on the couch and exploring my thoughts and emotions, because it showed me how difficult it is to change something in oneself and that we should not ask patients to understand and respectively change something in their life, which we cannot do ourselves, specifically since this is also not linked to the underlying pathophysiology of their diseases.

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

During my academic studies and experience, I needed to listen to the patients carefully, taking into account the existing scientific literature. I also communicated this to my students and younger colleagues. I was often reminded of the saying of Louis Pasteur from 1854, "In the field of observation, chance favours only the prepared mind". With this in mind, the development of new underlying mechanisms for the better understanding of the patient can be developed in a back-translational manner.

Please tell us more about your most relevant focal points – past or present – within your chosen field of science.

Earlier studies dealt with the effect of light therapy in seasonal affective disorder (SAD), and interestingly, a patient once correctly informed me that this disease should be called light deficiency disorder instead of seasonal affective disorder (SAD). This inspired me to conduct a study in São Paulo, Brazil, in which we could demonstrate that higher rates of depression emerged during the rainy monsoon season, coinciding with light deficiency in the working population. During my time at the psychiatric department at the University of Bonn in Germany with my longtime good friend Hans-Jürgen Möller as chair, we had a close collaboration with neurologists as well as neurosurgeons. A colleague from the Department of Epileptology once informed me that patients are quite happy after undergoing transcranial magnetic stimulation (TMS) to identify an epileptogenic focus, which helps guide neurosurgeons during planned operations. I asked my colleague if side effects accompany this method, and after he assured me that this is not the case, he performed this TMS methodology on me. He set the coil on my right hemisphere, and I realized that the left thumb was moving without my will. I did not have any changes in my mood, since I was also not depressed, and there were no side effects.

Thereafter, we introduced this methodology first to depressed patients and witnessed an antidepressant response. However, publishing these results was quite challenging, but we managed to do so. I was pleased to see that TMS developed excellently, and it is often overlooked that our roots in psychiatry are in my group in Bonn, Germany. Together with my team at the Medical University in Vienna, we conducted a large number of neuropsychopharmacological studies, and nearly all medications currently on the market were studied in our group, mostly within multicenter trials, demonstrating efficacy and fewer side effects compared to the older compounds. In schizophrenia, an additional benefit for depressive and so-called negative symptoms could be demonstrated.

More recently, I have been focusing on treatment-resistant depression (TRD) and working with a European group on this topic (GSRD: group for studies of resistant depression). We sampled over 3000 patients in different European countries and recorded clinical as well as biological variables. We could show that symptoms like severity, anxiety, and suicidality within depression, as well as the number of previous episodes, are linked to TRD. We performed whole genome analysis, and it looks like the structures that we are usually interested in, the monoamine transporters or serotonin receptors, do not show any genetically differentiating pattern in patients who respond or do not respond to antidepressant treatment. Based on our studies, we also defined treatment-resistant depression, not responding to two antidepressant trials, irrespective of mechanisms of action, given in sufficient length and dosage, as TRD patients. We were pleased that the European health regulatory authorities (the EMA) also adopted this definition. Several studies, including those for the development of intranasal esketamine, utilized our definition and subsequently brought this medication to market.

What were the key impact areas of your research topics?

The key impact areas of my research were always patient-centered. Early studies covered topics on psychopathology, such as catatonia. I could show that patients with malignant catatonia are not treated anymore by psychiatrists but in internal medicine and therefore are not vanished. A large number of studies have been carried out in neuropsychopharmacology, such as the introduction of the serotonin-reuptake inhibitors (SSRIs) as well as atypical antipsychotics for schizophrenia. A part of my research was also related to phytopharmacology. I insisted to the groups I worked with that phytopharmacological compounds should be studied in the same manner as chemical substances, and based on this approach, St. John's Wort, as well as Silexan, a standardized Lavandula extract, exhibited positive results in randomized controlled trials for depression and anxiety disorders, respectively.

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

I thoroughly enjoyed the discussions and collaborations with bright, often young colleagues who questioned what was so clear to me. I was enthusiastic to see how rigorously they performed studies under my guidance. I also enjoyed organizing national and international congresses in Vienna and abroad. I founded the Austrian Association for Neuropsychopharmacology and Biological Psychiatry (ÖGPB), and I was the president of the World Federation of Societies of Biological Psychiatry as well as the president of the Collegium Internationale Neuropsychopharmacolorum (CINP), both of which represent a worldwide research community for advancement of the knowledge in the field.

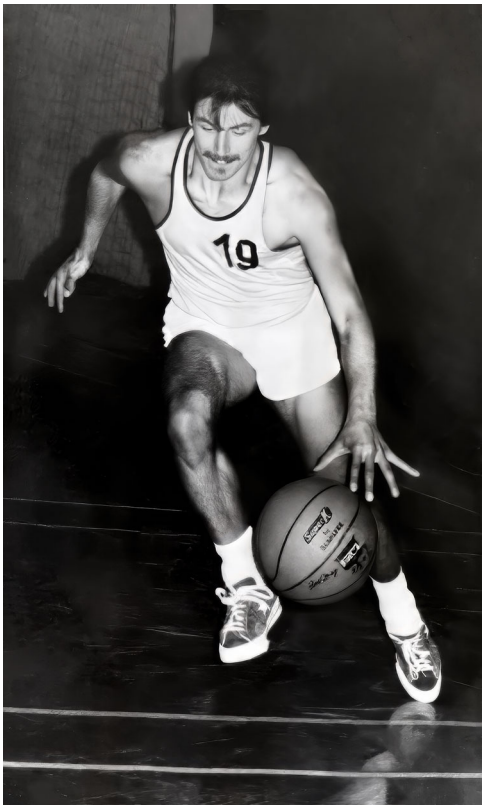

Figure 2. Siegfried Kasper in his youth as a point guard for an Austrian second division basketball team, wearing jersey #19. Despite being the smallest player on the team, his athletic background would later inform his understanding of psychological barriers to learning, as he observed while teaching skiing.

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 you feel strongly devoted to?
Most of my research has been carried out in Germany and Austria; however, during my stay at the National Institute of Mental Health, I also performed studies on US citizens. I was aware that cultural facets need to be considered when interpreting study results. For instance, I performed a study with a Japanese colleague comparing paranoid delusions in Japanese and German patients and realized how different the contents were; however, the structure of the delusions was identical.

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 nature, and I work with great pleasure in my garden and at my informal scientific outpost in southern Italy, specifically in Puglia, where I enjoy olive trees and maintain my small vineyard with primitivo grapes. Furthermore, I am thrilled to have a wonderful dog around me, always the same race. This Lakeland terrier brings me much joy through communication, and she reminds me that there are biological rhythms for activities like playing and walking. I have slowed down quite a bit with sports. However, when I was young, I was a basketball player in the Austrian second-highest league (see Figure 2). As the smallest player on the team, I mostly played point guard. Coming from Austria, of course, skiing was high on my mind. I was a ski instructor, and as a ski instructor, I probably did my first psychiatric interventions, because I could see very fast if a person was able to learn skiing or not, like having anxiety was always a negative predictor for learning to ski.

Part 2: YOUR NAME – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
I am impatient and always looking for new things. If I discovered something, I would lose interest and want to move on. Furthermore, I am stubborn and very determined. I never give up. When I have an idea, I want it to come to life.

Among your talents, which one(s) give(s) you a competitive edge?
Among my talents, the competitive edge is that I am always interested in new ideas, and if I reach a goal, I do not sleep on this pillow, but I am ready to embark on a new area.

If you could change one thing about yourself, what would it be?
I would change my impatience.

What is your current state of mind?
I think I am fine. I love to live and hope that this will go on for quite a while, since I am already approaching the age of 75, luckily without a severe disease.

What is your idea of perfect happiness?
Perfect happiness is like Sigmund Freud pointed out, the ability to work and love, and if you combine both of these things with the right persons and cultural environments, then the likelihood of having perfect happiness is very high.

When and where were you happiest? And why were so happy then?
I am always happy when I reach a goal, like when the NIMH invited me to be a fellow or when the scientific community voted for me as president of the World Federation of Societies of Biological Psychiatry. I was so happy because this indicated to me that I could proceed with another step in my life.

What is your greatest fear?
My greatest fear is having a severe illness that disables me.

What is your greatest regret?
My greatest regret is that I did not spend enough time with my loved ones.

What are you most proud of?
I am most proud of my academic achievements, which I share with my colleagues, and am always thrilled to meet again.

What do you consider your greatest achievement?
My most outstanding achievement was conducting studies that transformed the treatment and understanding of our patients.

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

Figure 3. Professor Siegfried Kasper (right) with colleague Hans-Jürgen Möller, former Chair of Psychiatry at Ludwig-Maximilians-University Munich and past President of the Collegium Internationale Neuro-Psychopharmacologicum (CINP), standing beside the bust of Emil Kraepelin, the pioneering psychiatrist who transformed psychiatry into a scientific discipline. Kasper considers Kraepelin one of his greatest inspirations, noting he "would love to have dinner with Emil Kraepelin because he shaped Psychiatry into a scientific discipline and he was already traveling all over the world."

What or who is your greatest passion?
My greatest passion is conducting research and helping to uncover mechanisms that improve the lives of psychiatric patients.

What is your favorite occupation (or activity)?
My favorite occupation is writing articles on psychiatric topics. Additionally, I enjoy giving lectures and traveling to different countries, where I hope to understand our common problems through discussions with colleagues.

What is your greatest extravagance?
My greatest extravagance is that I like to have new cars, which should be well-equipped with technical toys.

What is your most treasured possession?
My most treasured possession is likely our house, which I share with my wife, Anita, in the neighbourhood of Vienna, and another one in Puglia, southern Italy, which I affectionately call my scientific outpost. It is nestled in an olive grove. Furthermore, I am delighted to have old textbooks, and probably the most treasured book is "The Antomy of Melancholy" by Robert Burton, published in 1651. I was lucky to buy this book during a meeting in Chicago when I was a young doctor, which nearly ruined my financial budget.

Where would you most like to live?
I like where I am living right now. This is a perfect place.

What is the quality you most admire in people?
I admire people who are open, honest, and happy, and who are sometimes ready for a joke.

What is the trait you most dislike in people?
What I dislike most in people is dishonesty and playing dirty games, especially when they fail to uphold an agreement we have reached.

What do you consider the most overrated virtue?
The most overrated virtue is being spendable.

What do you most value in your friends?
I value my friends most when they are open and I can count on them.

Which living person do you most admire?
A schizophrenic patient of mine who arranged to live with the burden of his disease.

Who are your heroes in real life?
I greatly value Viktor Frankl, whom I was fortunate to meet in person while he was still alive.

If you could have dinner with any historical figure, who would it be and why?
I would love to have dinner with Emil Kraepelin because he shaped Psychiatry into a scientific discipline, and he was already traveling all over the world, including Indonesia (see Figure 3).

Who are your favorite writers?
Milan Kundera, Thomas Bernhard, Ernest Hemingway, and Erich Fried.

Who are your heroes of fiction?
I do not like fiction; I never read fiction.

What aphorism or motto best encapsulates your life philosophy?
Stay tuned and be the pilot of your life.

Vienna, Austria
18 August 2025

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MINI-REVIEW

Neuromodulation techniques in obsessive-compulsive disorder: Current state of the art

Brain Medicine September 2025;1(5):34–41; doi: https://doi.org/10.61373/bm025y.0125

Keywords: DBS, neuromodulation, OCD, rTMS, tDCS

Obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric condition often resistant to conventional treatments such as cognitive behavioral therapy and pharmacotherapy. For treatment-refractory cases, neuromodulation techniques offer promising alternatives. This review provides an overview of recent advances in three major neuromodulation strategies: transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS). DBS has demonstrated robust efficacy across several brain targets, though clinical outcomes are influenced by interindividual variability in fiber anatomy, lead positioning, correct parameter adjustments, and symptomatology. Recent efforts focus on connectivity-based targeting, patient-specific imaging, and the development of closed-loop systems guided by electrophysiological and neuroimaging biomarkers. rTMS, a noninvasive neuromodulation technique, shows therapeutic potential but lacks consensus on optimal parameters and cortical targets, despite FDA approval of certain stimulation protocols. tDCS, while the most accessible modality, presents inconclusive evidence due to small sample sizes and heterogeneity in electrode montages. Overall, these neuromodulation techniques are rapidly evolving and hold considerable promise, but further high-quality studies are needed to standardize stimulation protocols, validate reliable biomarkers and tailor interventions to individual patient profiles. Personalized neuromodulation may represent the future of therapeutic strategies in OCD.

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by persistent, intrusive thoughts and dysfunctional, repetitive, and ritualized behaviors (1). It typically manifests in childhood or adolescence and is frequently accompanied by comorbid anxiety and depressive symptoms (2, 3). The lifetime prevalence of OCD in the general population is approximately 2%–3% and symptoms are commonly managed with cognitive behavioral therapy and pharmacotherapy (3–5). Although serotonin reuptake inhibitors are first-line treatments with demonstrated efficacy in OCD, up to 40%–60% of patients exhibit an inadequate response (6).

For these cases, neuromodulation techniques such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS) represent potential alternatives. These techniques may modulate the orbitofronto-striato-pallido-thalamic circuitry, encompassing the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC), and thalamus, that is dysfunctional in OCD (7, 8).

The aim of this invited review is to provide a summary of recent advances in these three major neuromodulation techniques and their effectiveness in treating patients with OCD.

Transcranial direct current stimulation

tDCS is a noninvasive brain stimulation procedure that may alleviate OCD symptoms by delivering low-intensity electrical current to specific brain areas via two scalp electrodes: an anode (excitatory) and a cathode (inhibitory) (9).

tDCS offers advantages over other neurostimulation approaches, including portability and relatively low cost, supporting the feasibility of home-based use (10, 11).

Anodal or cathodal tDCS modulates cortical excitability by depolarizing or hyperpolarizing neuronal resting membrane potentials, respectively, influencing synaptic transmission (9) and regional cerebral blood flow (12). In OCD, hyperactivity of cortico-striato-thalamo-cortical circuits, including the caudate nucleus, the OFC, the anterior cingulate cortex (ACC) (13) and the subthalamic nucleus (STN) (14, 15), has been implicated in symptomatology. Through cortical neuromodulation, tDCS may attenuate this hyperactivity, contributing to symptom improvement.

Synaptic plasticity—particularly long-term potentiation (LTP) and long-term depression—is central to learning and memory and its dysregulation has been associated with OCD (16, 17). The rationale for tDCS in OCD involves LTP-like mechanisms thought to modulate dysfunctional circuits (18, 19).

However, findings from meta-analyses evaluating tDCS in OCD remain inconclusive, due to small sample sizes, clinical heterogeneity of OCD and methodological inconsistencies, including unstandardized stimulation protocols and lack of neuronavigation (20).

Ibrahim *et al*., in their systematic review, reviewed randomized controlled trials (RCTs) involving 147 patients with OCD and found no significant difference between active and sham tDCS; surprisingly, sham tDCS was associated with greater symptom reduction, questioning the clinical value of tDCS for OCD (21).

Similarly, Pinto *et al*. reported no significant differences between active and sham stimulation (22). However, montages placing the primary electrode over the pre-supplementary motor area (pre-SMA) and an extracephalic reference generated stronger electric fields in OCD-relevant brain regions (22). These findings align with prior evidence showing that cathodal pre-SMA stimulation reduced symptoms, likely by downregulating pathological hyperactivity in this area (23).

Potential symptom reduction with tDCS without increased adverse effects was also observed in one study; however, the small sample sizes and methodological variability limit interpretability, underscoring the need for further high-quality trials (24).

Regarding stimulation targets, Silva *et al*. found modest improvements with SMA (25), whereas Fineberg *et al*. proposed the OFC as a potentially more effective target (26).

Given the limited evidence regarding the efficacy of tDCS in OCD, largely attributable to the considerable heterogeneity of stimulation protocols, which has led to divergent results across clinical trials (20), tDCS is not yet employed in clinical practice for the treatment of OCD. At this stage of evidence, reflection on the optimal protocol and target remains

Received: 31 July 2025. Revised: 11 October 2025. Accepted: 13 October 2025.
Published online: 28 October 2025.

premature from a clinical standpoint. Future studies should focus on standardizing stimulation parameters, including electrode placement, as well as session duration and frequency, in order to generate more robust findings and clarify whether this neuromodulation technique is truly effective in this disorder. The favorable feasibility and tolerability profile of tDCS makes it a promising technique for further investigation; although it cannot yet be recommended for routine clinical use, patient inclusion in clinical trials may be encouraged.

tDCS is generally safe, with adverse effects typically mild and transient. In a retrospective analysis of 171 subjects undergoing 2005 tDCS sessions, the most common adverse events were burning sensations (16.2%), skin redness (12.3%), and scalp pain (10.1%), followed by itching (6.7%) and tingling (6.3%), all rated as mild and transient, further supporting the overall safety of tDCS in clinical psychiatric settings (27).

Repetitive transcranial magnetic stimulation

rTMS is a noninvasive neuromodulation technique that alters brain activity using a magnetic coil generating a field through the scalp (28). Brain activity changes with stimulation frequency: low-frequency ($\leq$1 Hz) is generally inhibitory, whereas high-frequency ($\geq$5 Hz) is typically excitatory (29).

The therapeutic effect of rTMS in OCD is presumed to involve modulation of dysfunctional cortico-striato-thalamo-cortical circuits, aiming to normalize hyperactive areas like the OFC and SMA through inhibitory protocols or enhance hypoactive areas via excitatory stimulation, thus restoring network functional balance (30).

In 2018, the FDA approved rTMS for resistant OCD using a high-frequency deep stimulation protocol targeting the prefrontal cortex (PFC) and ACC (31, 32). In this pivotal multicenter RCT involving 100 participants, significantly more patients responded to active treatment (45.2%) compared to sham (17.8%), with response defined as a $\geq$ 30% reduction in yale-brown obsessive compulsive scale (Y-BOCS) scores (32). Interestingly, although high-frequency stimulation is typically excitatory, its application to the hyperactive mPFC/ACC did not appear to further worsen hyperactivity.

Beyond the mPFC/ACC, alternative targets have been investigated: bilateral and right DLPFC (34–36), as well as left DLPFC, SMA and OFC (34, 37, 38).

Despite numerous meta-analyses, consensus is lacking regarding optimal rTMS parameters for OCD, including frequency, target site, and duration (33). As summarized in Table 1, clinical outcomes vary considerably across stimulation targets and protocols. In practical terms, bilateral DLPFC and SMA protocols appear to yield the largest and most consistent improvements, whereas mPFC/ACC and OFC stimulations show more variable or time-limited effects, suggesting that clinicians should prioritize dorsolateral and motor network targets when selecting rTMS strategies for OCD (Table 1).

Liang *et al*. demonstrated the efficacy of low-frequency stimulation (LF-rTMS) over the SMA and DLPFC, while high-frequency rTMS (HF-rTMS) of the mPFC/ACC, despite being FDA-approved, did not show significant benefit (34). Conversely, Perera *et al*. found bilateral DLPFC stimulation, both LF or HF, more efficacious than other protocols (35).

Subsequent meta-analyses confirmed comparable efficacy across several protocols, including bilateral HF-rTMS of the DLPFC, bilateral LF-rTMS of the pre-SMA, right DLPFC LF-rTMS, and bilateral mPFC/ACC stimulation with both HF and LF frequencies (33, 36, 39). The OFC has also emerged as a potential target. LF-rTMS applied to the left OFC for 3 weeks led to significantly improved Y-BOCS scores at weeks 3 and 10 compared to control (40).

Regarding treatment duration, extending sessions beyond 4 weeks has not consistently added benefit (33). Other meta-analyses indicate that 10–20 sessions may suffice for therapeutic effect, with no clear gain from longer protocols (41, 42).

In terms of stimulation type, although theta burst stimulation (TBS) is time-efficient and theoretically potent, current clinical evidence does not support its efficacy in OCD. Harika-Germaneau *et al*. applied continuous TBS, an inhibitory protocol, over the SMA, but found no significant improvement relative to sham, possibly due to the low number of pulses (600) and subtherapeutic intensity (70% resting motor threshold [RMT]) relative to effective rTMS studies (43). Liu *et al*. delivered intermittent TBS, an excitatory protocol, to the DLPFC and compared it to 1 Hz rTMS over the SMA; again, no significant difference emerged. The authors noted limitations such as nonindividualized targeting and low session count (44). Furthermore, interindividual variability in neuroplastic response, potentially influenced by genetic factors such as the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism, may partly explain outcome heterogeneity, as proposed by Harika-Germaneau *et al*. and mechanistically supported in Chung *et al*. (2016), who demonstrated that BDNF genotype influences the direction and magnitude of TBS-induced plasticity (45).

On the other hand, the commonly held dichotomy of HF as excitatory and LF as inhibitory does not consistently predict changes in the activity of the targeted brain region. HF-rTMS may instead work by disrupting maladaptive circuit activity (31), as seen in other neuropsychiatric disorders, such as epilepsy (46). This variability underscores the complexity of brain dynamics, with outcomes influenced by baseline excitability, individual differences and circuit state during stimulation.

Furthermore, the accelerated rTMS protocol, involving multiple HF stimulation sessions per day over a condensed period (e.g., 5 days), aims for faster and stronger clinical effects. The Stanford SAINT protocol, which applies ten sessions of intermittent TBS daily, guided by individualized functional magnetic resonance imaging targeting, has demonstrated rapid efficacy in treatment-resistant depression (47). To date, no accelerated rTMS protocols with comparable intensity, frequency or proven efficacy have been established for OCD. This may reflect inconsistent TBS outcomes in OCD, potentially due to subtherapeutic stimulation parameters and lack of individualized targeting.

Due to difficulties in predicting clinical outcomes based solely on stimulation frequency or target region, there is increasing support for personalizing rTMS protocols based on individual neurophysiological profiles. rTMS may benefit from personalized target selection and stimulation parameters (48, 49).

The level of evidence supporting the efficacy of rTMS in OCD is moderate to high, making it a viable clinical option for treatment-refractory cases before considering more invasive techniques, namely DBS, particularly when balancing the risks and benefits of each intervention (50).

rTMS is generally safe and well-tolerated. The most serious adverse effect, seizure, is rare and usually associated with HF stimulation or predisposing neurological conditions (51). More commonly, side effects are mild and transient, including scalp discomfort, tension-type headaches, tingling or auditory sensitivity from the clicking noise, all usually resolving without the need to discontinue treatment (51).

Deep brain stimulation

DBS has supplanted ablative neurosurgical procedures and is indicated for patients with treatment-resistant OCD (52). The technique entails the implantation of electrodes in a specific deep brain target, connected to a pulse generator that delivers electrical stimulation (52). In 2009, the FDA granted DBS for OCD a Humanitarian Device Exemption.

The most common targets for OCD are: the anterior limb of the internal capsule, (ALIC), ventral capsule/ventral striatum (VC/VS), nucleus accumbens (NAc)—noting that these three regions often refer to anatomically overlapping regions, caudate nucleus and the bed nucleus of the stria terminalis (BNST) (53), a component of the extended amygdala that is heavily interconnected with the ventral striatum and involved in anxiety and compulsive behavior regulation. These structures constitute components of cognitive-affective circuits involved in reward processing, motivational regulation and compulsive behavior (53).

Clinical trials have demonstrated the efficacy of DBS targeting these structures. In 2010, Denys *et al*. conducted an RCT of ALIC-NAc stimulation, achieving full response in 9 of 16 patients with a mean reduction of 46% in Y-BOCS scores (54). Subsequently, Luyten *et al*. carried out a double-blind crossover study in 17 patients implanted with a single electrode per hemisphere targeting the ALIC-BNST region. Although

Table 1. Summary of rTMS targets, protocols, and clinical outcomes in OCD treatment

Target	Stimulation Type	Outcome	Study	Study Type
Bilateral DLPFC[a]	LF[b]- or HF[c]-rTMS	Both significantly superior to sham; larger effect size than other protocols (left DLPFC, right DLPFC, SMA[d], OFC[e] or mPFC[f]) with Hedge's g of 1.04	Perera *et al*., 2021	Meta-analysis (26 RCTs[g])
	HF-rTMS	Superior to sham; DLPFC and mPFC/ACC protocols more likely to be among the highest-ranked interventions	Vinod *et al*., 2024	Meta-analysis (33 RCTs)
	HF-rTMS	More efficacious than sham with Hedge's g of 0.90; similar efficacy to LF-rTMS of right DLPFC and LF-rTMS of bilateral pre-SMA	Fitzsimmons *et al*., 2022	Meta-analysis (21 RCTs)
Right DLPFC	LF-rTMS	Superior to sham	Vinod *et al*., 2024	Meta-analysis (33 RCTs)
	LF-rTMS	More efficacious than sham with Hedge's g of 1.03; similar efficacy to HF-rTMS of bilateral DLPFC and LF-rTMS of bilateral pre-SMA	Fitzsimmons *et al*., 2022	Meta-analysis (21 RCTs)
Left DLPFC	LF-rTMS	More efficacious than sham; Y-BOCS weighted mean difference of 6.34 compared to sham; might be the most effective intervention among all rTMS strategies for OCD treatment	Liang *et al*., 2021	Meta-analysis (22 RCTs)
	HF-rTMS	More efficacious than sham; Y-BOCS weighted mean difference of 3.77 compared to sham	Liang *et al*., 2021	Meta-analysis (22 RCTs)
Bilateral mPFC/ACC[h]	HF-dTMS	More efficacious than sham; reduction of 6 points in Y-BOCS in the active group vs 3.3 points in the sham group	Carmi *et al*., 2019	RCT (99 subjects)
	HF or LF-rTMS	Superior to sham; DLPFC and mPFC/ACC protocols more likely to be among the highest-ranked interventions	Vinod *et al*., 2024	Meta-analysis (33 RCTs)
mPFC/ACC	HF-rTMS	Not more efficacious than sham, despite FDA approval	Liang *et al*., 2021	Meta-analysis (22 RCTs)
Bilateral pre-SMA	LF-rTMS	More efficacious than sham with Hedge's g of 0.56; similar efficacy to LF-rTMS of right DLPFC and HF-rTMS of bilateral DLPFC	Fitzsimmons *et al*., 2022	Meta-analysis (21 RCTs)
Bilateral SMA	LF-rTMS	Superior to sham	Vinod *et al*., 2024	Meta-analysis (33 RCTs)
SMA	LF-rTMS	More efficacious than sham; Y-BOCS weighted mean difference of 4.33 compared to sham	Liang *et al*., 2021	Meta-analysis (22 RCTs)
	LF-rTMS	More efficacious than rTMS over DLPFC or OFC with Hedge's g of 1.68 for SMA and 0.97 for LF-rTMS	Rehn *et al*., 2018	Meta-analysis (18 RCTs)
	LF-rTMS	More efficacious than sham with Hedge's g of 1.37 for SMA and OFC and 0.8 for LF-rTMS	Berlim *et al*., 2013	Meta-analysis (10 RCTs)
OFC	LF-rTMS	Not more efficacious than sham	Liang *et al*., 2021	Meta-analysis (22 RCTs)
	LF-rTMS	Significant but time-limited improvement compared to sham; Y-BOCS reduction of $\geq$25% for 50% of the subjects and $\geq$35% for 25% of the subjects	Ruffini *et al*., 2009	RCT (23 subjects)
	LF-rTMS	More efficacious than sham with Hedge's g of 1.37 for SMA and OFC and 0.8 for LF-rTMS	Berlim *et al*., 2013	Meta-analysis (10 RCTs)

Hedge's g values were recoded so that positive values indicate superiority of active treatment over sham.
[a]DLPFC: dorsolateral prefrontal cortex.
[b]LF: low frequency.
[c]HF: high frequency.
[d]SMA: supplementary motor area.
[e]OFC: orbitofrontal cortex.
[f]mPFC: medial prefrontal cortex
[g]RCT: randomized controlled trial.
[h]ACC: anterior cingulate cortex.

the electrode trajectory allowed anatomical coverage of both areas, stimulation was delivered either to ALIC or to BNST depending on the activated contact. The study reported a 53% response rate and a 37% median improvement during the blinded phase; during the open-label phase, 67% of patients were full responders, with a 58% median reduction in Y-BOCS scores. Notably, patients with active contacts in BNST showed significantly greater improvement than those stimulated in ALIC (55). More recently, Mosley *et al*. replicated these results in a randomized, double-blind, sham-controlled trial involving 9 patients using ALIC-BNST stimulation, finding a statistically significant difference from sham ($p = 0.025$),

Table 2. Summary table has been adapted from Raviv *et al*. (2020), integrating data from RCTs and high-quality case series investigating various DBS targets for treatment-resistant OCD. Evidence levels and GRADE categories reflect the quality and strength of the findings across studies. Anatomical overlap and variability in target nomenclature are noted where relevant

Target	Main Findings	Level of Evidence	GRADE	Notes
BNST[a]/ALIC[b]	Significantly reduced OCD[c], anxiety and depressive symptoms; improved global functioning. Long-term safety up to 14 years.	II	High	One electrode can anatomically cover both targets; clinical effects differ by contact site.
STN[d]	Reduced Y-BOCS by ~41%; increased positive emotional ratings; improved global functioning. Effects on depression/anxiety variable.	I–III	High-Moderate	Potential for motor/limbic symptom targeting; cognitive flexibility may improve.
NAc[e]	Median 50% symptom reduction in responders. Often overlaps with caudate/VC/VS[f] regions.	II–III	High–Moderate	Target for reward-related symptoms, but anatomical boundaries often overlap with VC/VS.
Caudate nucleus	35% to 60% Y-BOCS reduction in small studies; improvements associated with decreased caudate hyperactivity.	III	Low	Targeted in small series; often combined with NAc stimulation.
VC/VS	Reduced Y-BOCS and improved functioning. Effects similar to STN in some trials.	II–III	Moderate-Low	Overlaps with ALIC and NAc; inconsistent nomenclature across studies.
ITP[g]	~50% Y-BOCS decrease; promising but limited evidence.	III	Moderate-Low	Uncommon target; potential role in emotion regulation.
Gpi[h]	Dramatic improvement in vocal tics and OCD in all 4 patients in small series.	III	Moderate	Rarely used; explored for overlap between OCD and Tourette.

[a]BNST: bed nucleus of the stria terminalis.
[b]ALIC: anterior limb of the internal capsule.
[c]OCD: obsessive-compulsive disorder.
[d]STN: subthalamic nucleus.
[e]NAc: nucleus accumbens.
[f]VC/VS: ventral capsule/ventral striatum
[g]ITP: inferior thalamic peduncle.
[h]GPi: globus pallidus internus

along with a 50% mean Y-BOCS reduction and 78% response rate during the open phase (56). Provenza *et al*. further confirmed these effects in an open-label phase followed by cognitive behavioral therapy and a double-blind withdrawal: all 5 participants responded fully with a 55% mean Y-BOCS reduction; symptoms recurred upon DBS cessation and remitted upon reactivation, affirming the causal role of stimulation (57) (Table 2).

The STN is a well-established DBS target in treatment-refractory OCD, with reported Y-BOCS reductions from 33 to 21.8 with a 67% response rate in one study (15) and from 28 (sham) to 19 with 75% response in another study (14), using $\geq$ 35% Y-BOCS reduction as the response criterion (Table 2).

Other investigated targets include the anteromedial globus pallidus internus (amGPi), currently a DBS target for Tourette syndrome with encouraging findings for OCD symptoms (58), the inferior thalamic peduncle (53), the lateral habenula, the superolateral medial forebrain bundle (59) and the zona incerta (60). However, for these targets, evidence is still limited and further studies are needed to evaluate the efficacy in treating OCD (Table 2).

It is increasingly recognized that DBS targets overlap anatomically and stimulation effects may depend on activated tissue volume (53). These targets are embedded in interrelated networks governing behavior, dysfunction of which may underlie OCD symptoms (61). Tractography and connectivity analysis have been proposed to define optimal DBS pathways (62), though no consensus exists on a specific white matter tract. Proposed white matter targets include the medial forebrain bundle (63), the fronto-thalamic tract (64) and the hyperdirect pathway between the PFC and the STN (65).

Given substantial interindividual variability in fiber anatomy, advanced patient-specific imaging is imperative (66). Symptom dimensions, such as checking or contamination, appear to activate distinct prefrontal regions (67). Barcia *et al*. found that optimal stimulation contacts exhibited stronger connectivity with prefrontal areas activated by symptom provocation (68). On the other hand, Tyagi *et al*. observed that STN-DBS preferentially improved cognitive symptoms whereas VC/VS-DBS alleviated depressive features (15). Finally, Li *et al*. proposed a common therapeutic pathway originating in the ALIC, connecting to the dorsal ACC and ventrolateral PFC and culminating in the anteromedial STN, potentially underlying core OCD symptom relief, with additional pathways necessary for specific symptom clusters (65).

Although normative connectomes derived from healthy populations facilitate network mapping, they fail to capture individual anatomical variability or disease-driven alterations (69). For instance, the distinct tracts traversing the ALIC link the PFC to the thalamus, ventral tegmental area and STN (70, 71) and display considerable individual anatomical variability (66, 70), possibly explaining heterogeneous ALIC-DBS outcomes and reinforcing the need for patient-specific imaging before defining stimulation targets (69, 72). Nonetheless, normative maps remain useful when individual data is unavailable (62).

Recent work has challenged the concept of fixed anatomical "target," proposing instead that DBS acts by modulating a common functional network engaged across multiple stimulation sites. In a large connectomic analysis, Li *et al*. demonstrated that effective stimulation sites, regardless of anatomical location, converged on a unified network encompassing the ACC, precuneus, mPFC, and insula. This shift from a "valid target" to a "valid network" paradigm suggests that optimal outcomes may

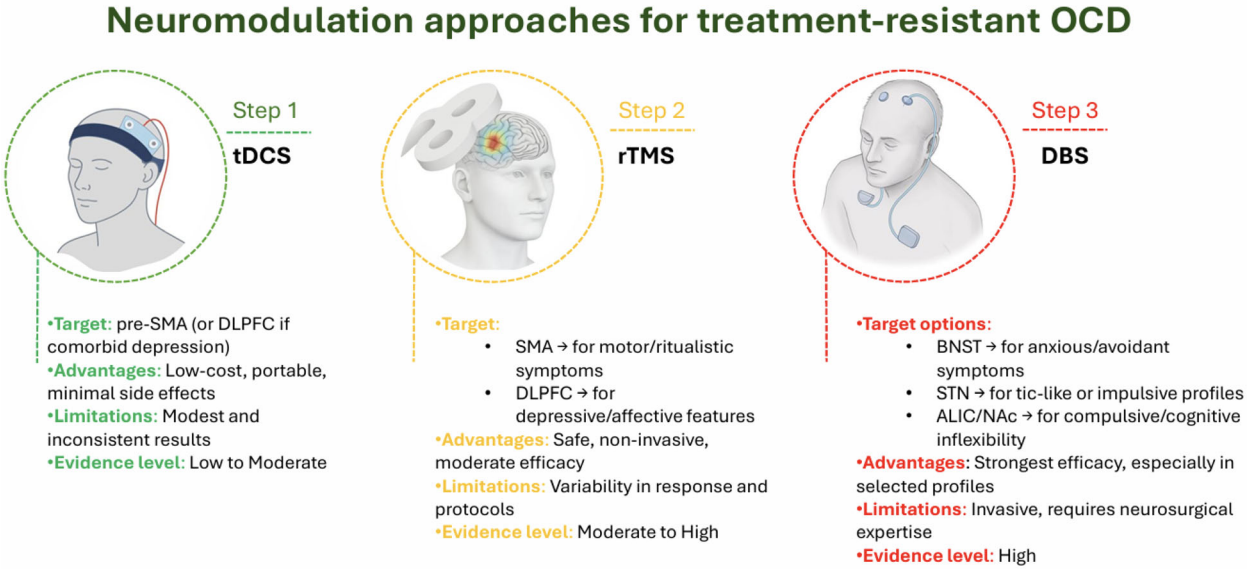

Figure 1. Pre-SMA: Pre-Supplementary Motor Area; DLPFC: Dorsolateral Prefrontal Cortex; SMA: Supplementary Motor Area; BNST: Bed Nucleus of the Stria Terminalis; STN: Subthalamic Nucleus; ALIC: Anterior Limb of the Internal Capsule; NAc: Nucleus Accumbens. This figure outlines a proposed sequential algorithm for neuromodulatory interventions in treatment-resistant obsessive-compulsive disorder. Rather than being organized strictly by evidence level, this framework prioritizes a gradient of clinical feasibility and invasiveness, moving from the least to the most invasive approches.

depend more on the connectivity profile of the stimulated region than on its anatomical label (73).

Biomarker-guided personalization of DBS is an emerging framework with predictive potential (74). A significant challenge in OCD is the temporal dissociation between electrophysiological changes and clinical response, unlike Parkinson's disease, for example, where real-time suppression of STN beta activity correlates with symptom relief (75). Psychiatric DBS typically requires months for symptom amelioration during parameter optimization (52, 76).

In OCD, electrophysiological biomarkers like local field potentials (LFPs) remain unclear. Theta and delta frequency bands are most studied but lack consistent clinical correlation (77). A case report suggested that identifying the contact with the highest beta activity peak could optimize clinical outcomes for DBS in the VC/VS (78). Provenza *et al*. observed a negative correlation between delta power and symptom severity (57) and Nho *et al*. associated low-frequency intracranial electroencephalogram (EEG) signals (<15 Hz) with obsessive thought episodes (79).

There is also interest in STN functioning in OCD, driven by prior Parkinson's disease research. Investigations in STN functioning have revealed burst-like LFP patterns in both groups (80); theta activity during emotional stimuli correlated with OCD severity (81); increased STN oscillations during symptomatic states and reduced gamma/beta activity in the right ventral STN have been reported (82) and Fridgeirsson *et al*. described individualized LFP signatures within the NAc, ventral ALIC and globus pallidus externus (83).

Emerging evidence suggests that STN DBS may exert disease-modifying effects through modulation of BDNF signaling, potentially supporting neuroplasticity and functional restoration. Although primarily studied in Parkinson's disease, these mechanisms may inform understanding of STN-related circuit modulation in OCD, guide therapeutic strategies and provide a line of investigation to account, at least partially, for the heterogeneity of clinical outcomes despite identical stimulation targets (84).

Furthermore, intraoperative observations of smiling and facial expression changes elicited by VC/VS stimulation have been linked to favorable outcomes and may guide electrode placement (85, 86).

A recent preclinical investigation utilizing a closed-loop optogenetic approach in Sapap3-knockout mice—a validated OCD model—demonstrated that real-time detection of low-frequency delta signals in the OFC triggered activation of striatal parvalbumin-positive interneurons, effectively interrupting compulsive grooming (87). This result provides a potential mechanistic foundation for closed-loop DBS in human OCD.

In conclusion, biomarkers are crucial for optimizing neuromodulation and implementing closed-loop DBS (52, 65).

Closed-loop neurostimulation systems offer a novel approach by continuously adjusting stimulation parameters based on real-time biomarker feedback (88). Contrary to traditional open-loop systems with fixed settings, closed-loop models cater to the fluctuating nature of neuropsychiatric disorders by using electrophysiological or neurochemical indicators to tailor therapy automatically (88).

The efficacy of such systems depends on identifying robust neuropsychiatric biomarkers. EEG and LFPs monitoring enable real-time assessment of brain activity and evaluation of stimulation effects, guiding postimplantation parameter tuning (89). However, no biomarker has yet been definitively linked to changes in mood (89). Indeed, adapting DBS parameters in response to symptom fluctuation may improve outcomes and reduce side effects with lower energy consumption (89). Closed-loop DBS has been shown to monitor LFPs in real time and modify stimulation to further reduce obsessive thoughts and compulsive behaviors while mitigating acute mood-related side effects, including hypomania (90).

Nonetheless, implementing closed-loop DBS entails significant challenges, including ensuring biomarker specificity to accurately reflect clinical state, employing rigorous signal filtering to prevent erroneous adjustments and achieving high temporal resolution to promptly adjust stimulation in response to neural dynamics (88).

DBS is associated with adverse effects in approximately 4.8%–7.7% of cases (91). The most serious complication is intraoperative hemorrhage, although it occurs in less than 1% of procedures. Electrode misplacement and intracranial infections are more common and are among the leading causes of device removal. Postoperative seizures are rare and typically linked to edema around the electrode. Stimulation-induced side effects most notably hypomania, typically resolve with parameter adjustment, although weight gain, insomnia, memory impairment, and anxiety have also been reported (92, 93). Other concerns relate to suicidality; the relationship between DBS and increased suicidality remains debated and may reflect the baseline severity of illness or unmet expectations (94, 95).

In contrast to movement disorders treated with DBS, neuropsychiatric illnesses treated with DBS lack immediate symptomatic improvement,

making it much more complicated and time-consuming to reach optimal parameters. Indeed, improvements in OCD symptoms and anxiety may take weeks, several months, or even years to be achieved, whereas Parkinsonian rigidity or tremor resolves in a few seconds or minutes in front of the examiner programming the DBS.

In clinical practice, given that DBS is an invasive procedure, it is reserved for cases of treatment-refractory OCD (50). Nevertheless, the current evidence regarding its efficacy is the most consistent and robust when compared with the other two techniques.

Conclusion

Neuromodulation techniques such as tDCS, rTMS, and DBS hold significant promise, particularly for patients with treatment-refractory OCD. DBS, although more invasive, has demonstrated clinical efficacy in reducing OCD symptoms across various brain targets. Nevertheless, clinical responses remain heterogeneous, largely due to anatomical variability and differences in symptom dimensions. Moving forward, the field will likely be shaped by advances in personalized neuromodulation. Critical priorities include the development of robust electrophysiological biomarkers, individualized tractography to optimize target selection and the implementation of adaptive closed-loop stimulation systems capable of dynamically tailoring treatment. In contrast, while rTMS and tDCS offer less invasive alternatives, they face certain limitations. rTMS lacks consensus regarding optimal stimulation parameters and target regions and the efficacy of tDCS in OCD remains a subject of debate due to methodological shortcomings and variability in electrode montages. In summary, these neuromodulation strategies are advancing rapidly, but further high-quality research is required to optimize protocols. Ultimately, harmonization of trial design, coupled with biomarker-guided and patient-specific approaches, will be essential to personalize neuromodulation and to maximize the therapeutic potential of these techniques in OCD.

Author contributions

KSL and CV conducted the conceptualization, data curation, investigation, methodology, resources, visualization, writing – original draft and writing – review and editing. KSL also conducted the project administration and supervision. LM conducted the conceptualization, methodology, validation, writing – original draft and writing – review and editing. JFA, JE, JFB, JB, PV, EMM, BPM, PV, and AVG conducted the conceptualization, methodology and writing – review and editing.

Funding sources

PV was funded by a grant from the Swiss National Science Foundation. KS-L and BPM have received funding from the Department of Psychiatry at the Lausanne University Hospital for academic advancement and research time. BPM has received funding from the Fondation Anna & André Livio Glauser and from the UNIL (Université de Lausanne) through the "Tremplin" grant from the "Bureau de l'Egalité" for academic advancement and research time.

Author disclosures

KS-L has been regularly participating in paid advisory boards and training activities for J&J since 2023.

The contributors have confirmed that no conflict of interest exists.

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THOUGHT LEADERS INVITED REVIEW

Rethinking the impact and management of electroconvulsive therapy session number in depression

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Electroconvulsive therapy (ECT) has been an essential treatment for severe depressive disorder, utilizing electrical current to induce generalized seizures under anesthesia. Session is one of the core parameters of ECT, yet critical knowledge gaps persist regarding its quantitative relationships with clinical outcomes and neurobiological mechanisms, while lacking consensus on optimal stopping rules. This narrative review focused on the impact of ECT session on depression improvement, memory impairment, seizure duration, and biomarkers, representing antidepressant efficacy, cognitive safety, neurophysiological processes and mechanisms of ECT. Building on multidimensional analyses, we propose a novel response-guided sequential strategy that tailors ECT sessions and sequential treatments through individual therapeutic responses, optimizing early antidepressant effects while avoiding ineffective or excessive sessions. Comprehensive mapping of ECT session effects in clinical will establish predictive frameworks for ECT response optimization, catalyzing a paradigm shift from empirical to algorithmic depression therapeutics.

Brain Medicine September 2025;1(5):42–51; doi: https://doi.org/10.61373/bm025i.0053

Keywords: Biomarkers, cognitive impairment, depressive improvement, electroconvulsive therapy, seizure duration, sequential treatment, sessions

Introduction

Electroconvulsive therapy (ECT) is one of the oldest surviving biological forms of neurostimulation for severe or medication-resistant depression in which brief and generalized seizures were induced by electrical current (1). Its origins date back to the advent of modern biological psychiatry in 1938. Over time, a series of refinements encompassing electrode placement, pulse width, muscle relaxants, and anesthetics have significantly enhanced its efficacy and safety profile while concurrently reducing side effects (Figure 1). Presently, ECT is administered under meticulous medical and psychiatric supervision and remains a well-established acute treatment option for depression. It produces response rates of 60%–80%, surpassing those of alternative antidepressant therapies (2, 3). Despite its propensity to induce cognitive impairment, ECT is widely used in clinical settings, with approximately 1 million people receiving ECT annually. However, fundamental questions regarding ECT remain unanswered. A primary concern for patients undergoing ECT pertains to the number of sessions deemed necessary and appropriate for their condition.

ECT is a treatment modality that relies on a series of sessions. Most national guidelines recommend a course of 6 to 12 sessions over 2 to 4 weeks, typically resulting in the alleviation of depressive symptoms (4, 5). The total number of sessions is determined by the ECT team, depending on patient's the severity of depression and clinical response. However, there are doubts regarding these sessions. On one hand, the recommended number of sessions is based more on clinical experience than on scientific evidence. Due to the widespread and longstanding acceptance of ECT, there is a tendency to believe accumulated clinical impressions as if they were incontrovertible facts. On the other hand, the number of treatment sessions varies widely among clinics and psychiatrists owing to inconsistent standards, with some patients receiving a higher than average number of ECT sessions (6). In academic terms, the outcomes of ECT are influenced by the number of sessions, which researchers may overlook (7). Moreover, any efforts to improve ECT, such as the calculation of dose delivery, exploration of electrode configurations, selection of anesthetics, and utilization of electromagnetic energy in magnetic seizure therapy, are closely intertwined with the determination of the number of treatment sessions (Figure 2) (8, 9). In summary, irrespective of patient-specific considerations, scientific research rigor, or technological development demands, the number of sessions remains a pivotal parameter and avenue for advancement in ECT. Therefore, it is crucial to understand the patterns of ECT sessions comprehensively. This is a guidance for clinicians and reassurance for patients seeking credible treatment options.

In this narrative review, our focus lies on exploring the impact of the number of ECT sessions. First, from a clinical perspective, we discuss the trajectories of depression improvement and memory impairment during ECT, as these factors constitute key cognitive variables crucial for understanding the effect of ECT (Figure 3) (10). Subsequently, we delve into the evolving trend in epileptic seizure duration, a parameter believed to be pivotal for achieving a successful antidepressant outcome through ECT from a methodological standpoint (11). Furthermore, we analyzed longitudinal studies involving hematological and magnetic resonance imaging (MRI) assessments during ECT to investigate how the brain responds to increasing ECT sessions (12). Additionally, the sequential treatment strategy combines different intervention methods to maximize the advantages of each therapy and reduce the side effects or residual symptoms of a single treatment, offering a promising approach for improving depressive disorder outcomes (13). Therefore, we propose an innovative ECT optimization framework, the ECT response-guided sequential strategy, which beyond conventional protocol extensions, instead developing dynamic sequential treatment plans based on individualized ECT response trajectories. We hope this systems-level evidence and model will motivate future research, ultimately leading to a comprehensive understanding and facilitating more effective ECT practices.

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Received: 4 February 2025. Revised: 27 April 2025 and 1 May 2025. Accepted: 3 May 2025.

Published online: 3 June 2025.

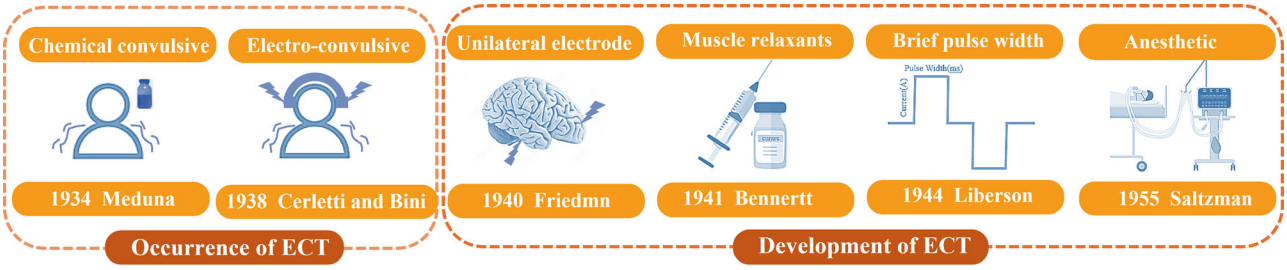

Figure 1. The historical milestone for the evolution of ECT. ECT originated from chemical drug induced epilepsy and gradually developed into modern ECT in terms of electrode placement, muscle relaxants, pulse width, and anesthetic parameters.

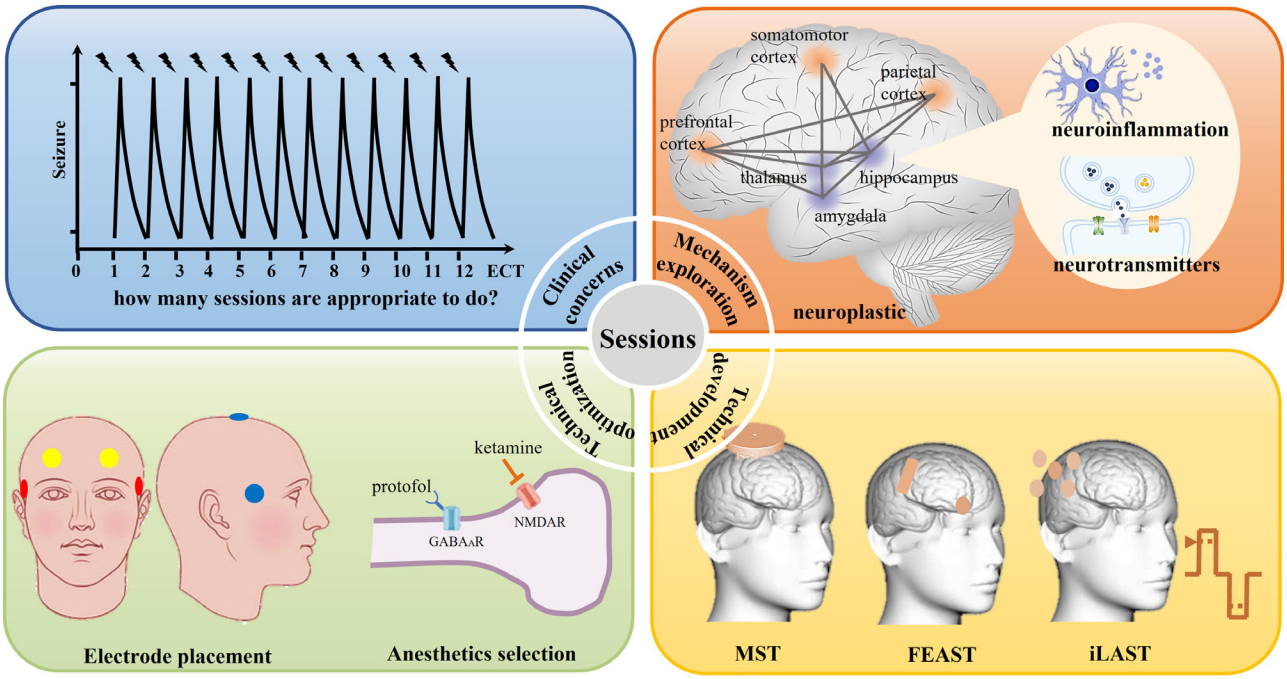

Figure 2. The central role of ECT sessions. The central role of ECT sessions in clinical problem, mechanism exploration, technical optimization, and technical development. MST, magnetic seizure therapy; FEAST, focal electrically administered seizure therapy; iLAST, individualized low amplitude seizure therapy.

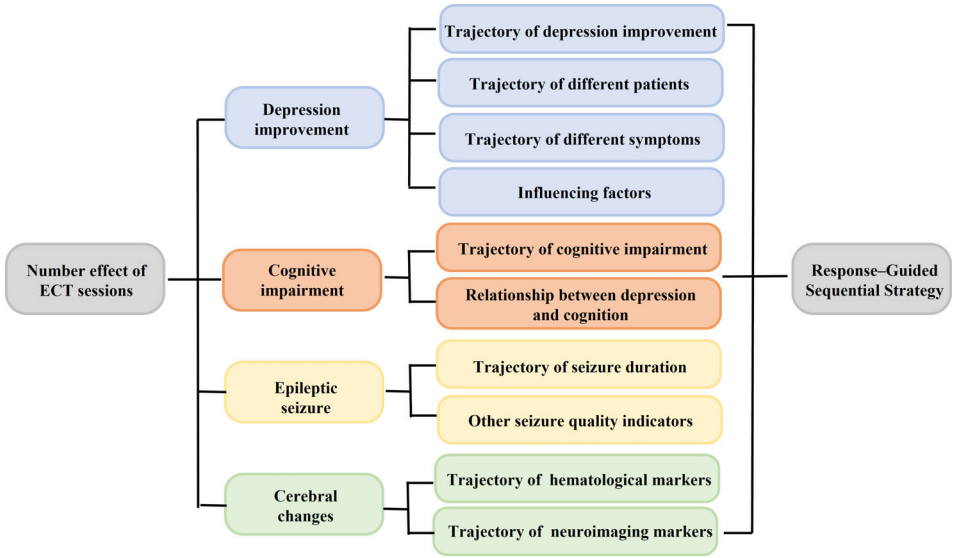

Figure 3. The conceptual framework of this review. The discussion framework of this review based on the effects of ECT sessions.

Search Strategies and Selection Criteria

Evidence for this narrative review was identified through searches of PubMed, Cochrane Library, Embase, ClinicalTrials.gov and relevant references in those articles with the search terms: "electroconvulsive therapy" AND ("depression" OR "depressive") AND ("session" OR "course" OR "trajectory") AND ("response" OR "remission") AND ("cognitive" OR "cognition") AND ("seizure") AND ("hematological" OR "biomarker") AND ("neuroimaging" OR "MRI") AND ("sequential treatment"). Articles published in English up to October 31, 2024 were included.

Trajectory of Depressive Improvement

Depression is a common and disabling psychiatric disease accompanied by high suicide attempts (14, 15). Although ECT has significant advantages over antidepressants in efficacy and course, clinicians and patients seek clarity regarding the pace at which clinically meaningful benefits manifest, which defined as either achieving remission (i.e., an asymptomatic state) or response (i.e., a $>$ 50% reduction in baseline symptoms severity), or reaching a plateau (i.e., no change in depression score). For example, what is the extent of depression improvement after each ECT session? when does the response or remission onset? What is the discrepancy in the speed of remission across different dimensions of depression? Which situations have a more rapid response following ECT?

Investigators have documented a nonlinear antidepressant response pattern over ECT. the Consortium for Research in ECT (CORE) conducted significant research in this field, gathering Hamilton Rating Scale for Depression (HRSD) scores after each ECT in 576 patients (16, 17). Their findings revealed a notable decrease in the mean HRSD score by 25.8% after the first session, 39% after the second session, and 49.3% after the third sessions. It was observed that the median time to first response was typically three ECT sessions, with remission achieved after approximately four additional ECT sessions, demonstrating an early improvement trajectory. Other studies have similarly reported rapid effects of ECT in comparable populations. In the Prolonging Remission in Depressed Elderly (PRIDE), involving 185 geriatric depressed patients received right unilateral ECT, the mean decrease of HRSD scores in the first three ECT sessions were 24.5%, 35%, and 42.7%, respectively (18). Additionally, Rodger *et al.* reported the change in HRSD score between first and third session was six times greater than the remaining sessions (19). Overall, the trajectory of depressive improvement during ECT appears to be swift in the early stages, leveling off in the later stage, reflecting the relatively rapid response to ECT.

While average trajectories offer valuable insights, substantial individual differences remain in the speed of response to ECT. Clinical case reports have described varied response patterns, including rapid response after one session and delayed improvement following 10 sessions (20, 21). A large prospective cohort study reported that 12.6% of patients responded after the first session, whereas 5.9% showed no response throughout the treatment course (16). Another study found that 40% patients recovered with two to four ECT sessions, 40% with five to eight sessions, and only 20% required nine to 12 sessions (22). To better characterize the variability, researchers have applied data-driven methods to identify distinct response subgroups. Latent class analysis of 156 consecutive patients identified five distinct trajectories of depressive symptoms, including rapid improvement (25%), moderate improvement (30.12%), slow improvement (19.23%), slow improvement with delayed onset (11.54%), and no improvement (12.82%) (23). Similarly, growth mixture modeling in 239 patients identified three patient groups consisting of rapid response group (16.74%), slow response group (76.15%), and nonremit group (7.11%) (24). Taken together, these studies underscore the heterogeneity in ECT response trajectories. Recognizing and accounting for these variations may help guide individualized treatment duration, optimize outcomes, and reduce unnecessary exposure to prolonged ECT courses.

As widely acknowledged, depression is a heterogeneous disease characterized by multiple distinct symptom clusters, including mood, anxiety, somatic, insomnia symptoms, and suicidal ideation, among others (25). When treating depression, it is essential to recognize that not all symptoms improve at the same rate or degree (26). Relying solely on total scores of depressive symptom severity to define responses may lack detection of resolved and residual symptoms. Some studies have suggested that suicidal ideation respond quickly to ECT (27), hence proposing suicide risk as an indication for ECT. In contrast, a study involving 89 older persons with depression found that while all dimensions showed rapid and significant improvement, the mood dimension demonstrated the highest rate of improvement compared to suicidal dimensions (28). These results are consistent due to the differing proportions of each dimension in the HRSD scale; for example, the suicidal dimension comprised only one item. Considering the covariation of symptoms over time, a dynamic time warping analysis of 68 participants showed that improvements in somatic symptoms and suicidal ideation preceded those in mood symptoms (29). In conclusion, the temporal trajectories of symptom clusters vary, and it remains debatable which sets of symptoms are most effectively and rapidly targeted.

In addition to subgroup analyses of response trajectories, several studies have investigated predictors of early and delayed responses to ECT. Notably, patients with bipolar depression, psychotic features, and higher depression severity at baseline showed a more rapid response after ECT (24, 30). There is evidence that among initial responders, patients with unipolar depression require an average of six treatments to meet the response criteria. In contrast, patients with bipolar depression meet the response criteria after four treatments (30). In the CORE study, patients with psychosis had an average percentage change in HRSD of 64% compared to 56% for nonpsychotic groups after the fifth ECT (31). Additionally, a regression model demonstrated that baseline HRSD scores were significantly associated with a rapid response. Other clinical characteristics also affect response speed. Treatment-resistant depression (TRD) is often associated with slower improvement, while comorbid personality disorders are linked to a higher likelihood of nonresponse (23). In contrast, first-episode depression does not appear to significantly influence response speed (23). The role of age in response speed is inconsistent and complex. While some studies indicate that elderly patients experience faster remission than younger patients (32), another study reported that elderly patients with depression require more ECT treatments than adults (33). This discrepancy arises from various factors interfering with the analysis of the independent role of age. Regarding the ECT technique, response speed is associated with electrode placement (34). Kellner *et al.* observed a decrease of 44% in HRSD scores after the first session of right unilateral ECT, 48% for bifrontal ECT, and 51% for bitemporal ECT (35). Despite growing insights into potential predictors, systematic evidence on the temporal dynamics of ECT response remains scarce, as most meta-analyses emphasize overall outcomes (36, 37). Future studies should investigate how clinical and technical factors shape response trajectories, to support more personalized and effective ECT protocols.

Trajectory of Cognitive Impairment

Cognitive impairment is a frequent adverse effect of ECT among patients, which can be divided into memory-related and nonmemory cognitive impairment (38). Memory-related issues include disorientation, anterograde amnesia and retrograde amnesia. Nonmemory cognitive impairment involves decreased attention, processing speed, and executive function (39). National guidelines recommend the cognitive impact of ECT should be monitored on an ongoing basis. However, in clinical practice, key questions remain unanswered: when does the cognitive impairment occur? Does the trajectory of cognitive impairment worsen or improve over time? What is the relationship between depressive symptoms and cognitive impairment?

Cognitive deficits emerge early in ECT (40). A prospective follow-up study found that 62% of patients with depression reported subjective memory deficits after the first ECT session, a figure that increased with subsequent ECT sessions (41). Although these deficits typically resolve after all modified ECT sessions are completed, 34% of the deficits may last for 6 months or longer (42). Notably, disorientation commonly surfaced immediately after the second ECT session and was more pronounced after the fifth ECT session (43). However, these results are somewhat subjective due to the nonspecific learning effects associated with cognitive measurement tools, hindering accurate assessment post-ECT. To address

these limitations, some researchers have adopted strategies such as employing multiple parallel sets of tests or reducing the frequency of measurements. Viswanath *et al.* applied a short cognitive-related battery in 30 inpatients and they found that objective cognitive deficits such as verbal memory, autobiographic memory, and psychomotor speed progressively deteriorated from the first to the third to the sixth ECT session (44). However, this study lacked a baseline assessment. Another study compared a new electroconvulsive therapy cognitive assessment (ECCA) tool with the classic Montreal Cognitive Assessment (MoCA). It indicated that ECCA scores were significantly decreased across the three testing points, whereas MoCA scores did not vary significantly (45). An intensive longitudinal follow-up of associative memory at five timepoints found that memory impairment occurred after the first ECT and worsened during subsequent ECT treatments (46). It is important to note that cognitive deficits are influenced by factors such as age, education level, and medications, including anesthetics and antidepressants. For instance, older individuals with lower education levels tend to experience more severe cognitive impairment (46), while substances like propofol, low-dose ketamine, and lithium may have potential cognitive-protective effects (47–49). In summary, cognitive impairment occurs early during ECT and may accumulate throughout the treatment course, implying the importance of understanding the optimal number of ECT sessions to mitigate unnecessary cognitive damage.

Emotion and cognition constitute the two main elements of neuropsychology (50). Despite ECT induces rapid improvement in depressive symptoms alongside cumulative cognitive impairment, the relationship between depression and cognitive function remains unclear. Clinical perspectives suggest that cognitive impairment might aid depressive remission by enabling patients to forget distressing memories (51). Bai *et al*. found that negative memory impairment was more severe than positive memory impairment and correlated with symptom relief (10). Conversely, depressive remission can enhance certain cognitive functions, such as increased subjective initiative (39, 52). From a neurophysiological perspective, the seizures induced by ECT, especially those aimed at enhancing efficacy, are often linked to cognitive side effects. For instance, compared to ultra-brief pulse width, brief pulse width has proven to be more efficacious regarding symptom reduction but resulting in more pronounced cognitive side effects (53). Right unilateral ECT typically yields milder and less persistent cognitive effects but slower response rates compared to bilateral ECT due to reduced stimulation of the left temporal lobe (54). Additional research suggests that hippocampal changes caused by ECT are involved in both depressive improvement and cognitive impairment (55). In conclusion, while emotion and cognition are closely connected, the exact nature of this relationship, the role of epileptic seizures, and the whole-brain alterations need further investigation. Before clarifying these questions, regular monitoring of both depressive symptoms and cognitive function during ECT is essential to help clinicians decide the optimal time to end treatment.

Seizure Trajectory

The objective of ECT is to induce generalized seizures, leveraging neurological changes that counteract those seen in epilepsy and psychiatric disorders. Various studies indicate that the effectiveness of ECT stems from generalized seizures surpassing the therapeutic benefits of noninvasive brain stimulation without convulsions (56). A typical ECT stimulus comprises a series of pulses ranging 100–1000, each lasting 0.25 to 1.0 ms, and an electrical silence of 6 to 16 ms between pulses, ultimately producing a seizure lasting 20 to 60 s (57). Despite its widespread use, several questions regarding ECT-induced seizures persist in clinical practice. For instance, how can the seizure quality be evaluated? What range is considered optimal? How does seizure quality change with an increase in the number of ECT sessions? And what is the relationship between seizure quality and therapeutic and cognitive outcomes?

Seizure duration has long been investigated as an important intermediate variable in determining dose–response properties due to its measurability through movement or electroencephalography (EEG). Evidence suggests an inverse correlation between the number of treatments and seizure duration (58). Rasimas *et al*. conducted a review of the course of ECT in 519 patients, and they found that seizure duration experienced the most significant drop between the first and second treatments, with a slight further increase thereafter (59). Similarly, a 17-year retrospective cohort study conducted at a single center, which enrolled 3648 patients receiving 32,879 courses of ECT treatments, reported a reduction in mean seizure duration across the course, with the greatest decrease in duration over the first three sessions (60). Research suggests that the reduction in seizure duration during ECT may be associated with an increased seizure threshold, shifts in the brain's inhibitory-excitatory balance, and adjustments in treatment parameters such as dosage (61–63). However, the potential implications of shorter seizures on the antidepressant properties of ECT remains controversial. A cohort study involving 6998 patients finding that patients with an EEG seizure duration of 60 to 69 s from the first ECT session had the highest remission rates compared to those with a seizure duration of less than 20 s (64), which suggests declining seizure duration signals treatment resistance. In contrast, other studies have indicated that higher electrical charges are associated with shorter seizure durations and higher remission rates (60). Some observational studies have also found no association between seizure duration and treatment response (65), which may simply reflect normal physiological adaptation. It is important to note that the current conflicting evidence on seizure duration and ECT outcomes largely stems from overreliance on first-session data, which fails to account for the process of change that unfolded over the treatment course. Moreover, there is no consensus regarding the minimum seizure duration required for ECT. Despite this, clinicians often endeavor to lengthen seizures in patients experiencing short seizure durations, with concerns that excessively brief seizures may be clinically ineffective (59). In summary, seizure duration as a pragmatic but incomplete guide shows an early decline during ECT, while further research is needed to clarify its relationship with clinical outcomes.

In addition to seizure duration, several ictal parameters derived using more complex algorithms based on the amplitude of the ictal EEG have been developed to assess seizure quality. These parameters include the average seizure energy index (ASEI), postictal suppression index (PSI), and seizure quality index (SQI), among others (66, 67). The ASEI and PSI are computed directly from the ECT device, the ASEI by multiplying the mean integrated amplitude with the seizure duration and the PSI by dividing the mean amplitude after seizure termination by the mean amplitude obtained during seizure. On the other hand, the SQI refers to the summed score of five different seizure domains, including duration, inhibition, amplitude, sympathetic activation, and interhemispheric coherence, at the second ECT session, to predict clinical outcomes (67). However, despite the existence of these parameters, there is a notable gap in research exploring the changing trends of these indicators during each ECT treatment and their relationship with clinical improvement and cognitive side effects. In addition, several factors can potentially affect variations in seizure quality, such as anesthetic use, stimulus dosage, electrode positioning, time of seizure induction, and medication, among others (62). Therefore, these variables must be combined or controlled to determine the trajectory of changes in seizure quality. Overall, the assessment of seizure quality during each ECT treatment session holds direct and significant clinical implications. Adjusting these indicators within defined limits makes it feasible to ensure session adequacy and, therefore, enhance the likelihood of a favorable clinical outcome.

Trajectories of Hematological and Neuroimaging Markers

Understanding the mechanisms of treatment responses is paramount for improving depression outcomes. However, due to its spatially unfocused nature, the neural mechanisms underlying the clinical response to ECT remain uncertain (68). Various hypotheses have been proposed to explain the effect of ECT, including neurotransmitter, neuroendocrine, neuroinflammation, and neuroplastic changes (12). For instance, monoamine neurotransmitter systems, such as norepinephrine, and inhibitory neurotransmitter systems, such as gamma-aminobutyric acid (GABA), have been discussed as potential mediators of therapeutic response in ECT (11). Additionally, ECT triggers the release of neurotrophic factors, adrenocorticotrophic hormones, and inflammatory mediators, including

interleukin-6, and cortisol (69). Moreover, ECT brings about widespread changes in the structure and function of the brain, attributed to neuroplastic effects (70). Although these effects are easy to detect, challenges persist in research on ECT-induced neurological effects. For example, questions arise regarding the temporal relationship between these neurological changes following ECT and the treatment effects. Moreover, there is a need to understand the internal relationship among these factors and determine which of these changes may be related to the antidepressant and amnesic effects or incidental phenomena.

Most existing studies have investigated neural alterations before and after ECT, which is the total effect of multiple ECT sessions, resulting in key changes being masked (71, 72). However, few studies have focused on the time course and processes of neural effects during ECT treatment. Regarding hematological markers, a longitudinal study spanning nine visits during the ECT period indicated that serum brain-derived neurotrophic factor (BDNF) levels increased after each ECT session yet showed no significant association with treatment response (73). Similarly, an exploratory study evaluated the acute endocrine effects and found that levels of cortisol and norepinephrine were significantly elevated after the first ECT session and fall back to baseline after the course of ECT (74). Another study by Göteson *et al*. investigated alterations in the serum proteome of 309 patients before and after the first ECT session and before the sixth ECT session, revealing findings related to signal transduction; however, none of the studied protein biomarkers were associated with the clinical response to ECT (75). In addition, no significant changes were found in white blood cell, proinflammatory cytokine/neurotrophin ratios, and plasma vascular endothelial growth factor levels over the course of ECT (76). In essence, on a finer time scale, the hematological markers associated with nutritional factors, inflammation, and endocrine function exhibit transient surges, potentially attributed to the stress induced by ECT.

In particular, because MRI is relatively safe without ionizing radiation, it has enabled repeated scanning of patients at various intervals to track the longitudinal trajectories of structural and functional cerebral changes during ECT. The majority of imaging studies are acquired before, mid and after treatment and focused on the hippocampus and the amygdala. Shantanu *et al*. scanned 43 patients with major depression at three timepoints: before ECT, after the second session, and within 1 week of completing the ECT series, and found progressive increases in hippocampal and amygdala volumes, which were associated with symptom improvement (7). Smaller baseline hippocampal volume predicted greater clinical response. Similarly, another longitudinal study of 14 patients, with MRI assessments conducted before ECT, after the fifth or sixth session, and at treatment completion, demonstrated a trend toward increased hippocampal volume across sessions. A large association analysis between MRI data and the number of ECT sessions from the Global ECT-MRI Research Collaboration (GEMRIC) reported a 0.28% linear increase in hippocampal volume after each ECT session (77–79). Marta *et al*. further examined hippocampal metabolites and amygdala functional connectivity across an acute course of bitemporal ECT including pretreatment, after the first and ninth sessions, and 15 days posttreatment, identifying sequential changes in neuroinflammatory markers and limbic network activity (80). These findings support the role of ECT-induced neuroplasticity in the hippocampus and amygdala in mediating clinical improvement in depression. Beyond the hippocampus–amygdala complex, longitudinal changes of gray matter volume or cortical thickness in the thalamus, putamen, and anterior cingulate cortex, as well as fractional amplitude of low-frequency fluctuations in the subgenual cingulate cortex and activation intensities within auditory networks have also been reported during ECT course. A summary of the longitudinal neuroplastic effects of ECT is provided in Table 1. Taken together, ECT appears to affect a broad range of brain regions, aligning with the distribution of electric field strength; however, its core neurobiological mechanisms remain unresolved (81). Moreover, findings from longitudinal studies suggest that ECT may induce brain changes at an early stage, consistent with the rapid clinical response. Nevertheless, the dynamic impact of ECT

Table 1. Longitudinal trajectories of neuroplastic effects during ECT in patients with depression[a]

Brain region	Analysis indicators	Timepoints during ECT	Longitudinal trajectory of neuroplastic effect	Correlation with outcome
Hippocampus (7, 80, 106)	Volume	Three timepoints (ECT0, ECT2 or ECT5, ECT endpoint)	Increase between each timepoint[a]	Relate to the clinical response
	Metabolite concentrations	Four timepoints (ECT0, ECT1, ECT9, ECT endpoint)	Decrease in NAA/Cr ratio and increase in Glx/Cr ratio at ECT9	Relate to the left hippocampus volume change
Amygdala (7, 82)	Volume	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between each timepoint	Relate to the clinical response
	Functional connectivity	Four timepoints (ECT0, ECT1, ECT9, ECT endpoint)	FC with lSgACC decreased between ECT1 and ECT9; FC with rDLPFC increased at ECT9	NA
Thalamus (83)	T2 relaxation Times	Three timepoints (ECT0, ECT1, ECT2)	Increase between each timepoint	Relate to the verbal anterograde memory impairment
Putamen (84)	Volume	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between ECT0 and ECT endpoint	NA
Anterior cingulate cortex (85)	Thickness	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between ECT0 and ECT endpoint	Relate to the clinical response
Limbic and paralimbic cortex (85)	Thickness	Three timepoints (ECT0, ECT2, ECT endpoint)	Increase between ECT0 and ECT endpoint	Not relate to the clinical response
Subgenual cingulate cortical (80)	fALFF	Three timepoints (ECT0, ECT1, ECT endpoint)	Decrease between each time point	A trend level correlation with clinical response
Auditory networks (86)	Activation intensities	Three timepoints (ECT0, ECT8, ECT endpoint)	Decrease between ECT0 and ECT 8, increase at ECT endpoint	Relate to the clinical response

[a]Changes during ECT are summarized qualitatively due to lack of reported effect sizes in original studies.
Note: ECT0 = prior to ECT; ECT1 = after the first ECT; ECT2 = after the second ECT; ECT5 = after the fifth ECT; ECT8 = after the eighth ECT; ECT9 = after the ninth ECT; ECT endpoint = after the entire ECT; fALFF = fractional amplitude of low-frequency fluctuations; NA = no data.

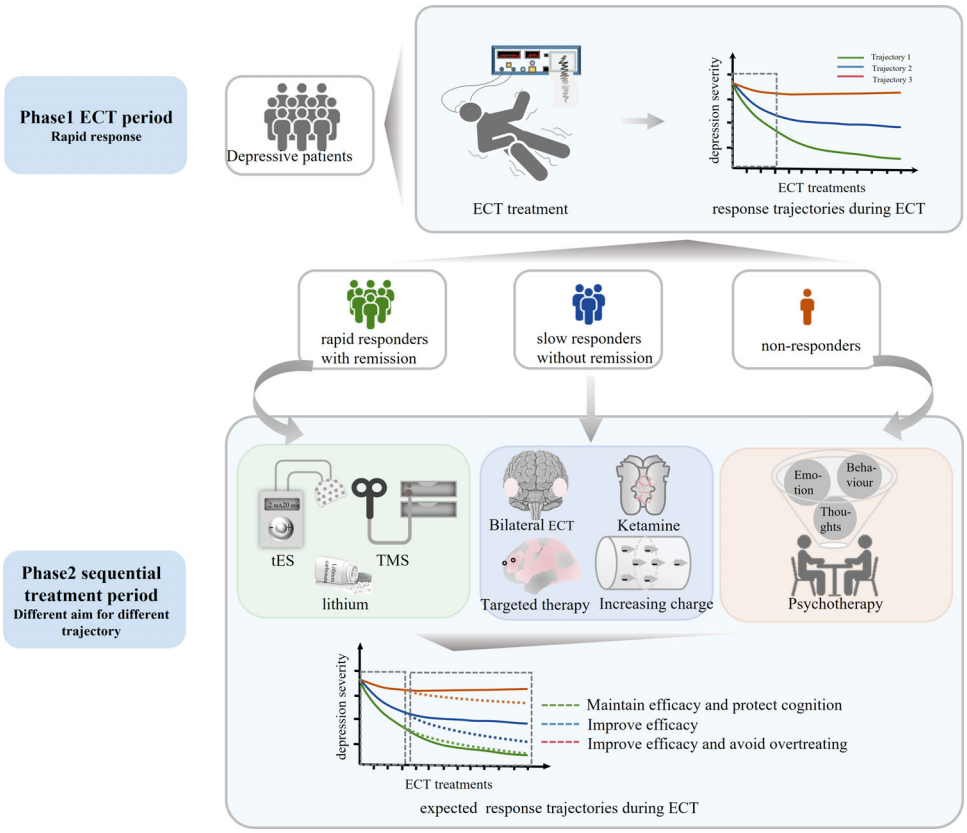

Figure 4. ECT response–guided sequential strategy. This strategy comprises two phases. In the initial phase, the goal is to exploit the advantage of ECT in rapidly inducing mood improvement and then to sequential reasonable treatment measures according to the response trajectories of different patients for maintaining efficacy and protect cognition, improving efficacy, and avoid overtreating. tES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation.

sessions on brain structure and function remains unclear, as most studies include only a limited number of observation timepoints, typically three or four. Notably, although longitudinal designs rely on self-comparisons, stimulation parameters, medications, and individual traits may still confound imaging findings, yet their effects remain insufficiently studied due to limited data. Therefore, further longitudinal studies using multi-dimensional imaging markers across more timepoints or even throughout ECT while controlling for potential confounding factors, are needed to generate a comprehensive profile of neuroplastic changes over time and their relationship to therapeutic outcomes (80–86).

The mechanism behind the early and rapid response to ECT remains elusive, with the microscopic changes in the brain that accompany these responses are still under speculation. Studies in rodents suggest that even a single ECT session can have profound effects, including the activation of the immune system and neurotransmitter increase. Hippocampal neurogenesis, which is thought to be involved in the therapeutic effects of ECT, was significantly increased in single electroconvulsive seizures in a rat model, consistent with the increased hippocampal volume shown by neuroimaging (87). However, some researchers argue that the induction of neurogenesis or an increase in gray matter volume takes time and may not occur acutely (20). Integrating insights from micro-level biology, meso-level imaging, and macro-cognitive levels at multiple timepoints could provide a clearer understanding of how the number of ECT sessions affect outcomes and further clarify the rapid onset mechanism of ECT.

ECT Response–guided Sequential Strategy

Although multiple treatment options are available for depression, no single treatment approach can fully and safely address the complexity of the disorder (13). In recent years, sequential treatment strategies, which combine different interventions in a staged and adaptive manner, have gained increasing attention (88). This approach aims to maximize the benefits of each treatment at a specific stage while minimizing the side effects and risk of treatment resistance that can develop from long-term use of a single treatment modality (89, 90). Therefore, a sequential treatment strategy is a meaningful shift in clinical thinking, allowing the selection of appropriate alternative treatment options based on the patient's response to the first course of treatment (91). In an ideal scenario, the primary objective of an initial ECT course is to treat the current episode while minimizing cognitive impairment. The number of sessions plays an important role in the clinical effects of ECT. Through our literature review, we have identified a discernible pattern in both depression alleviation and memory impairment throughout the course of ECT. Initially, depression tends to improve rapidly with successive ECT sessions, followed by a slower rate of improvement, while memory impairment tends to accumulate gradually. This supports the view that it may not be necessary to perform ECT so many times. Therefore, managing ECT sessions and sequencing to other treatments may be an effective way to improve outcomes (88, 92). The notable advantage of ECT lies in its swift antidepressant effect during the early stages, which is unmatched by other treatment modalities. However, as treatment progresses, the cognitive and economic burdens tend to escalate (93). In light of these considerations, we propose a new treatment strategy in which ECT should be terminated early once the optimal benefit-to-risk ratio is achieved, and then the patient should be transitioned to other safer treatments rather than persisting until complete remission. Notably, the response trajectories of ECT vary among patients with depression. Therefore, we outline an ECT response–guided sequential strategy to provide tailored sequential treatments for different response trajectories (Figure 4).

Based on the previously described speed of improvement and treatment outcomes, patients undergoing ECT can generally be categorized into three clusters: rapid responders with remission, slow responders

without remission, and nonresponders. Rapid responders with remission are those who improve quickly in the early stages of ECT. Although continued ECT can lead to remission, it may increase the risk of memory impairment. For these patients, sequential use of portable and safe noninvasive brain stimulation (NIBS) or lithium after an ECT-induced response helps consolidate the treatment effects while reducing cognitive damage (94). NIBS is an emerging therapy that modulates neuronal activity through physical stimulation, such as electricity, with the advantages of safety, portability, precise regulation, and cognitive enhancement, which is recommended by the FDA for the treatment of depression (95, 96). Sequential application of NIBS after ECT may not only further alleviate depressive symptoms through targeted modulation of specific brain regions, but also help prevent cognitive impairment caused by excessive ECT, protect cognition-related brain areas, promote cognitive recovery, and provide a home-based option that is more acceptable to patients (97–99). An adequately powered exploratory efficacy study is currently underway to provide definitive evidence of NIBS following ECT (100). Slow responders without remission are those who show a slow response in the early stages of ECT and experience no further clinical improvement in the later stages. This may be due to poor neural plasticity or insufficient precision of ECT (101). Augmentation strategies that lengthen seizure duration, such as applying bilateral ECT or increasing the electrical dosage, may improve efficacy, but at the expense of cognitive impairment (58). Alternatively, switching strategies may be considered, replacing ECT with fast-acting treatments such as ketamine, an N-methyl-D-aspartate antagonist, which has demonstrated rapid antidepressant effects and has been found to be noninferior to ECT (102). In addition, supplementation strategy using personalized neuromodulation therapies shows considerable promise in addressing individualized residual symptoms that may persist after ECT, such as anhedonia or somatic complaints. These symptoms are often not fully resolved by standard ECT protocols and may require targeted interventions tailored to specific neural circuits or symptom clusters, thereby complementing the antidepressant effects of ECT and enhancing overall recovery (103). The third group, a small subset of patients, showed minimal clinical response to ECT and were labeled nonresponders. The reason for poor efficacy is often due to the co-occurrence of personality disorders, making these patients more suitable for targeted psychotherapy or thought training (104). In summary, this response-guided sequential treatment strategy consists of two phases: an initial phase leveraging the rapid antidepressant effects of ECT, followed by tailored follow-up interventions based on individual response trajectories, such as maintenance, augmentation, switching, or supplementation, to optimize clinical outcomes while minimizing cognitive burden and overtreatment.

Although the theoretical foundation and indirect evidence supporting the sequential treatment strategy are compelling, further rigorous testing in future studies is essential. A key challenge lies in accurately characterizing individual ECT response trajectories and determining optimal sequential treatment approaches. Emerging evidence suggests that baseline predictors, including clinical characteristics (e.g., age, depression subtype, treatment resistance) and neuroimaging markers (e.g., hippocampal volume), may help forecast these trajectories and subsequent treatments, with further refinement of predictions achievable by integrating dynamic data, such as symptom reduction rates and biological changes during early treatment sessions (105). However, the reliable biomarkers and clinical features to guide transition decisions require investigation and validation in future studies. Another critical issue is determining the appropriate time to transition from ECT to subsequent interventions. Ideally, the cut-off point for ECT should be based on achieving optimal levels of neuroplasticity and disruption, providing a sufficient antidepressant response with minimal side effects (70). On average, responsive patients may require 3 to 4 ECT sessions to reach this critical point, while nonresponders should discontinue ECT, as it may no longer be suitable for them. It is important to note that this sequential strategy primarily addresses the acute treatment phase and does not replace the need for long-term consolidation, which is typically maintained with pharmacotherapy. Nevertheless, tailoring sequential treatment strategies based on ECT response trajectories holds significant potential for improving clinical outcomes, particularly by offering greater flexibility and safety in addressing challenging conditions such as TRD. We strongly encourage future clinical trials to further explore and validate this approach, ultimately enhancing understanding and improving treatment outcomes.

Conclusions

ECT, as a well-established neuromodulation technique, plays an important role in the treatment of severe depression. This review summaried the impact of ECT sessions on multiple therapeutic domains, including depression improvement, memory impairment, epileptic seizure time, and biological markers and highlighted the rapid early antidepressant effects of ECT alongside the cumulative risk of cognitive burden, underscoring the importance of managing treatment session. Taking into account the individual variability in treatment response, we proposed a response-guided sequential strategy that sequence other interventions based on distinct clinical trajectories to optimize outcomes. Although this approach remains hypothetical, it offers a testable framework that may generate new clinical trials and treatment options. We hope this review provides a conceptual and evidence-informed foundation to support individualized ECT decision-making and inspire future work in this field.

Author Contributions

Y.J. and Y.T. conceived and designed the review. Y.J. and H.Z. conducted the literature search. Y.J. and Y.W. created all the figures and tables. Y.J. wrote the first draft of the manuscript. W.K. and Y.T. critically revised the manuscript. The manuscript has been read and approved by all authors. All authors take full responsibility for all data, figures, and text, and approve the content and submission of the study.

Corresponding author: Professor Y.T. is responsible for all aspects of the work and for the submission process.

Funding Sources

This work was funded by the National Natural Science Foundation of China (No. 32071054 and No. U24A20702), and Anhui Province Clinical Medical Research Transformation Special Project (No.202204295107020006).

Author Disclosures

The authors have confirmed that no conflict of interest exists.

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RESEARCH ARTICLE

Exercise mitigates the effects of a cafeteria diet on antidepressant-like behavior associated with plasma and microbial metabolites in adult male rats

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A cafeteria diet high in saturated fat and sugar has been associated with increased anxiety-like and depressive-like behaviors and memory impairments, whereas exercise has been shown to promote antidepressant-like effects and enhance cognitive function in rodents. The mechanisms underlying the interactions between diet and exercise on mood, anxiety, and memory are not fully understood, but alterations in adult hippocampal neurogenesis (AHN), gut-derived metabolites, or plasma metabolic hormones may play a role. This study investigated whether voluntary exercise could mitigate the effects of concurrent exposure to a cafeteria diet on depression-like, anxiety-like, and cognitive behaviors in young adult male rats. Associated changes in AHN, metabolic hormones, and gut-derived metabolites were examined to identify potential mediators of behavioral changes. We found that exercise mitigated the cafeteria diet–induced increase in immobility in the forced swim test. This antidepressant-like effect of exercise in rats exposed to a cafeteria diet was accompanied by an attenuation of cafeteria diet–induced changes in plasma insulin and leptin, as well as in the abundance of caecal metabolites anserine, indole-3-carboxylate, and deoxyinosine. Exercise modestly improved spatial learning in the Morris water maze, promoted AHN and increased circulating levels of GLP-1, and these effects were blunted in animals exposed to a cafeteria diet suggesting that dietary composition plays a role in modulating the effects of exercise. Correlation analyses revealed that specific caecal metabolites were associated with depression- and cognition-related behaviors, independent of diet and exercise, highlighting the potential role of gut-derived metabolites in antidepressant-like behavior and cognitive function. Together these findings provide insight into potential metabolite and hormone-mediated mechanisms underlying the effects of a cafeteria diet and exercise on brain and behavior.

Brain Medicine September 2025;1(5):52–66; doi: https://doi.org/10.61373/bm025a.0116

Keywords: Western diet, exercise, hippocampal neurogenesis, depression, anxiety, cognition, metabolic hormones, gut microbial metabolites

Introduction

Increased availability of ultra-processed, energy-dense foods (1) and the prevalence of sedentary lifestyles (2) contributes to rising global ill health. A Western-style diet high in saturated fats and sugar, combined with inactivity, alters metabolic hormone concentrations (3–5), which causes obesity and increases the risk of depression, anxiety (6), and cognitive impairment (7, 8).

Rodent studies show that cafeteria (high-fat and high-sugar) diets, which mimic human Western-style diets, increase depression-like and anxiety-like behavior (9, 10), and impair recognition (11) and spatial memory (12). Conversely, exercise reduces anxiety-like and depression-like behavior and enhances pattern separation and spatial learning and memory (13–17). However, it remains unclear whether exercise can attenuate cafeteria diet–induced effects on depression-like, anxiety-like, and cognitive behaviors.

Adult hippocampal neurogenesis (AHN), the birth of new neurons in the dentate gyrus (DG) of the hippocampus, regulates anxiety-like behavior (18), pattern separation (19, 20), and spatial memory (21, 22), and is required for responses to antidepressants (23, 24). AHN is sensitive to external factors including diet and exercise (25), but these effects may be associated with age or sex. For example, adolescent-initiated cafeteria diet decreases AHN in male rats (26, 27), whereas the effects of adult-initiated cafeteria diet on AHN are unclear. However, the pro-neurogenic effects of exercise are well characterized in adult rodents (17, 28, 29). Importantly, both diet and exercise alter concentrations of metabolic hormones leptin (30), ghrelin (31), insulin (32), glucagon-like peptide 1 (GLP-1) (33), and fibroblast growth factor 21 (FGF-21) (34). These hormones influence AHN, suggesting possible mechanisms of lifestyle-mediated regulation of AHN and associated behaviors.

Diet and exercise are potent modulators of gut microbiota composition and microbial metabolism (35–39). Consumption of a cafeteria diet decreased microbiota diversity (40), and altered caecal metabolite composition in adult male rats (41). Conversely, exercise increased microbiota diversity (42, 43) and short-chain fatty acid (SCFA) production in the caecum (44). Microbial-derived metabolites including SCFAs, essential amino acids, and neurotransmitters (45) are now proposed as key mediators of the microbiota-gut-brain axis, significantly affecting AHN (35, 36). Notably, chronic disruption of the gut microbiota with antibiotics in adult male rats impaired AHN and associated behaviors (37), supporting previous evidence from germ-free mice of a role for gut microbiota in regulating AHN (38). Moreover, depression, anxiety, and Alzheimer's disease are associated with altered composition of gut microbial metabolites, with subsequent influences on AHN (46–49).

It remains unclear however if exercise attenuates the effects of cafeteria diet on AHN and associated behaviors. This study investigated if exposure of young adult male rats to voluntary wheel running exercise altered the effects of a cafeteria diet on AHN, depression-like, anxiety-like, and cognitive behaviors. Results provide insight into potential gut-derived or plasma-mediated metabolic mechanisms through which exercise may mitigate the effects of a cafeteria diet on brain and behavior.

Results

Exercise attenuated cafeteria diet–induced increases in body weight gain and adipose tissue

Both diet and exercise significantly affected body weight (Supplementary Figure S1A). Post-hoc analysis revealed that cafeteria diet increased weight gain in sedentary (CTRL-SED vs. CAF-SED, $p < 0.0001$) and to a lesser extent in exercising (CTRL-EX vs. CAF-EX, $p < 0.01$) animals.

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Received: 5 April 2025. Revised: 25 September 2025. Accepted: 26 September 2025.
Published online: 21 October 2025.

Interestingly, exercise significantly reduced body weight gain in cafeteria diet-fed animals (CAF-SED vs. CAF-EX, $p < 0.01$) but not in standard chow-fed animals (CTRL-SED vs. CTRL-EX, $p = 0.071$). Repeated measures ANOVA (analysis of variance) showed a significant effect of time and a diet–time interaction on average weekly running distance (Supplementary Figure S1B) but did not reveal a cafeteria diet–induced difference at any given week. Diet, exercise, and their interaction affected epididymal white adipose tissue (eWAT) weight (Supplementary Figure S1C). Cafeteria diet increased eWAT weight (CTRL-SED vs. CAF-SED, $p < 0.0001$; CTRL-EX vs. CAF-EX, $p < 0.01$), while exercise reduced it (CAF-SED vs. CAF-EX, $p < 0.0001$; CTRL-SED vs. CTRL-EX, $p < 0.01$). Finally, both diet and exercise independently affected brown adipose tissue (BAT) weight (Supplementary Figure S1D). Cafeteria diet increased BAT weight only in sedentary animals (CTRL-SED vs. CAF-SED, $p < 0.01$), and exercise reduced BAT weight gain in animals exposed to a cafeteria diet (CAF-SED vs. CAF-EX, $p < 0.05$).

Exercise mitigated a cafeteria diet–induced increase in immobility in the forced swim test and exerted a modest anxiolytic effect irrespective of diet

Because an unhealthy diet has been linked to changes in emotional behaviors, we tested whether exercise could influence the effect of a cafeteria diet on despair, anxiety, anhedonia, and locomotor activity. To measure antidepressant-like behaviors, animals underwent the forced swim test (FST) as previously described (50) (Figure 1B). There was a significant main effect of diet and exercise on the immobility score (Figure 1B, left panel). Cafeteria diet increased immobility in sedentary animals (CTRL-SED vs. CAF-SED, $p < 0.05$) which was mitigated in exercising rats (CAF-SED vs. CAF-EX, $p < 0.05$), suggesting an antidepressant effect of exercise. Swimming behavior was significantly affected by diet and exercise (Figure 1B, middle panel). Post-hoc analysis did not reveal significant differences between groups, although there was a trend to decrease swimming by cafeteria diet in exercising animals (CTRL-EX vs. CAF-EX, $p = 0.060$). Climbing behavior was not significantly affected (Figure 1B, right panel). In the elevated plus maze (EPM), there was a trend for an exercise-induced increase in the percentage of time spent in the open arms (anxiolytic effect, Figure 1C). Similarly in the novelty suppressed feeding (NSF), exercise alone significantly affected latency to eat (Figure 1D). Post-hoc comparisons showed that exercise decreased the latency to eat in standard chow-fed rats (CTRL-SED vs. CTRL-EX, $p = 0.0185$) but not in cafeteria diet–fed animals. To control for food interest which could confound the latency to eat, food intake was measured for each animal during the 30 min posttest (Figure 1E). Cafeteria diet tended to reduce posttest chow consumption in sedentary rats (CTRL-SED vs. CAF-SED, $p = 0.071$) and significantly in exercising rats (CTRL-EX vs. CAF-EX, $p < 0.001$). This suggests that supplementation with cafeteria diet decreased interest in standard chow. The lack of an exercise-induced effect on posttest chow consumption indicates that the reduced latency to eat was not due to increased interest in standard chow, but rather decreased anxiety-like behavior. Finally, animals were tested for anhedonia in the FUST (Figure 1F) and for locomotor activity and anxiety-like behavior in the open field test (OFT) (Figure 1G–H), yielding no significant effects.

There was a modest effect of exercise but not a cafeteria diet on spatial learning and memory

Pattern separation was evaluated in the modified spontaneous location recognition (MSLR) test (Figure 2A). There were no effects of diet or exercise in the large separation (low contextual overlap) test (Figure 2B, left panel), but both interventions tended to affect performance in the small separation [high contextual overlap (pattern separation)] test (Figure 2B, right panel). In the novel object recognition (NOR) test used to assess recognition memory, there were no effects of diet and exercise alone, although a diet–exercise interaction significantly affected the discrimination ratio (Figure 2C). Time and the time–exercise interaction significantly affected the latency to find the platform in the Morris water maze (MWM) over the 4 training days (Figure 2D). During the probe trial of the MWM, there were no effects of diet or exercise on the time spent in the target quadrant (Figure 2E), but there was a significant difference in the latency to the first visit to target quadrant (Figure 2F). Post-hoc analysis indicated that exercise increased the latency to reach the target quadrant in standard chow-fed (CTRL-SED vs. CTRL-EX, $p < 0.01$) but not in cafeteria diet–fed animals (CTRL-EX vs. CAF-EX, $p < 0.05$). There was a main effect of exercise on average velocity in the probe trial (Figure 2G). Exercise showed a trend to improve spatial learning and search strategies in the MWM in response to cafeteria diet or exercise (see Supplementary Materials and Supplementary Figure S2).

An exercise-induced increase in AHN is reduced by cafeteria diet

Neurogenesis was assessed across the longitudinal axis of the hippocampus using immunohistochemical staining of DCX, a marker of immature neurons in the DG (Figure 3B). There was a significant effect of exercise, and a diet–exercise interaction on the number of DCX^+ cells/mm^2 (Figure 3A, left panel). Post-hoc analysis revealed that the diet blunted (although not significantly) the number of DCX^+ cells/mm^2 in exercising animals (CTRL-EX vs. CAF-EX, $p = 0.086$). Thus, the neurogenic effect of exercise was observed only in standard chow-fed animals (CTRL-SED vs. CTRL-EX, $p < 0.001$). In the dorsal DG, exercise and the diet–exercise interaction significantly affected the number of DCX^+ cells/mm^2 (Figure 3A, middle panel),with post-hoc analysis showing that exercise significantly increased the number of DCX^+ cells/mm^2 in chow-fed animals (CTRL-SED vs. CTRL-EX, $p < 0.001$). In the ventral DG, there were significant main effects of diet and exercise on the number of DCX^+ cells/mm^2 (Figure 3A, right panel). Post-hoc analysis revealed that cafeteria diet blunted (nonsignificantly) the number of DCX^+ cells/mm^2 in exercising animals only (CTRL-EX vs. CAF-EX, $p = 0.068$) and exercise significantly increased the number of DCX^+ cells/mm^2 in chow-fed animals (CTRL-SED vs. CTRL-EX, $p < 0.05$).

Exercise attenuated a cafeteria diet–induced increase in the metabolic hormones insulin and leptin in plasma

Changes in metabolic hormones like glucagon-like peptide (GLP) 1, insulin, and leptin are linked with depression, anxiety and cognitive impairment (33, 51, 52). The cafeteria diet significantly increased insulin levels in sedentary animals in the current study (CTRL-SED vs. CAF-SED, $p < 0.001$) (Figure 4A), which was mitigated by exercise (CAF-SED vs. CAF-EX, $p < 0.05$). There was a significant increase in leptin after cafeteria diet in both sedentary (CTRL-SED vs. CAF-SED, $p < 0.0001$) and exercising animals (CTRL-EX vs. CAF-EX, $p < 0.01$) (Figure 4B). Exercise reduced leptin in standard chow (CTRL-SED vs. CTRL-EX, $p < 0.01$) and cafeteria diet–fed groups, (CAF-SED vs. CAF-EX, $p < 0.0001$). Cafeteria diet modestly increased total ghrelin (Figure 4C) and C-peptide (Figure 4D) in sedentary animals, with trends toward significance (ghrelin: CTRL-SED vs. CAF-SED, $p = 0.088$; C-peptide: CTRL-SED vs. CAF-SED, $p = 0.079$). The cafeteria diet increased FGF-21 (Figure 4E) in both sedentary (CTRL-SED vs. CAF-SED, $p < 0.001$) and exercising animals (CTRL-EX vs. CAF-EX, $p < 0.001$). On the other hand, total GLP-1 (Figure 4F) was increased in response to exercise (CTRL-SED vs. CTRL-EX, $p < 0.01$), which was reduced by cafeteria diet (CTRL-EX vs. CAF-EX, $p < 0.05$). Exercise elevated total PYY levels (Figure 4G) but in cafeteria diet–fed animals only (CAF-SED vs. CAF-EX, $p < 0.05$). Finally, glucagon (Figure 4H) was significantly reduced by cafeteria diet in exercising animals (CTRL-EX vs. CAF-EX, $p < 0.01$) and showed a trend toward reduction in sedentary animals (CTRL-SED vs. CAF-SED, $p = 0.085$).

Exercise attenuated a cafeteria diet–induced decrease in caecal metabolites anserine, indole-3-carboxylate, and deoxyinosine

Because a cafeteria diet and exercise can differentially alter gut microbiota compositions (39, 53, 54), we investigated whether the two interventions affected the caecal metabolome. This was also motivated by the observation that diet and exercise significantly affected the caecum weight (Figure 5A).

Principal component analysis from an untargeted metabolomics screen suggested an effect of cafeteria diet on the caecal metabolome (Figure 5B). Differential expression analyses revealed that the diet induced differential expression [false discovery rate (FDR)-adjusted $p < 0.05$] of 100/175 metabolites in sedentary animals (Figure 5C), while in exercising animals, cafeteria diet induced differential expression

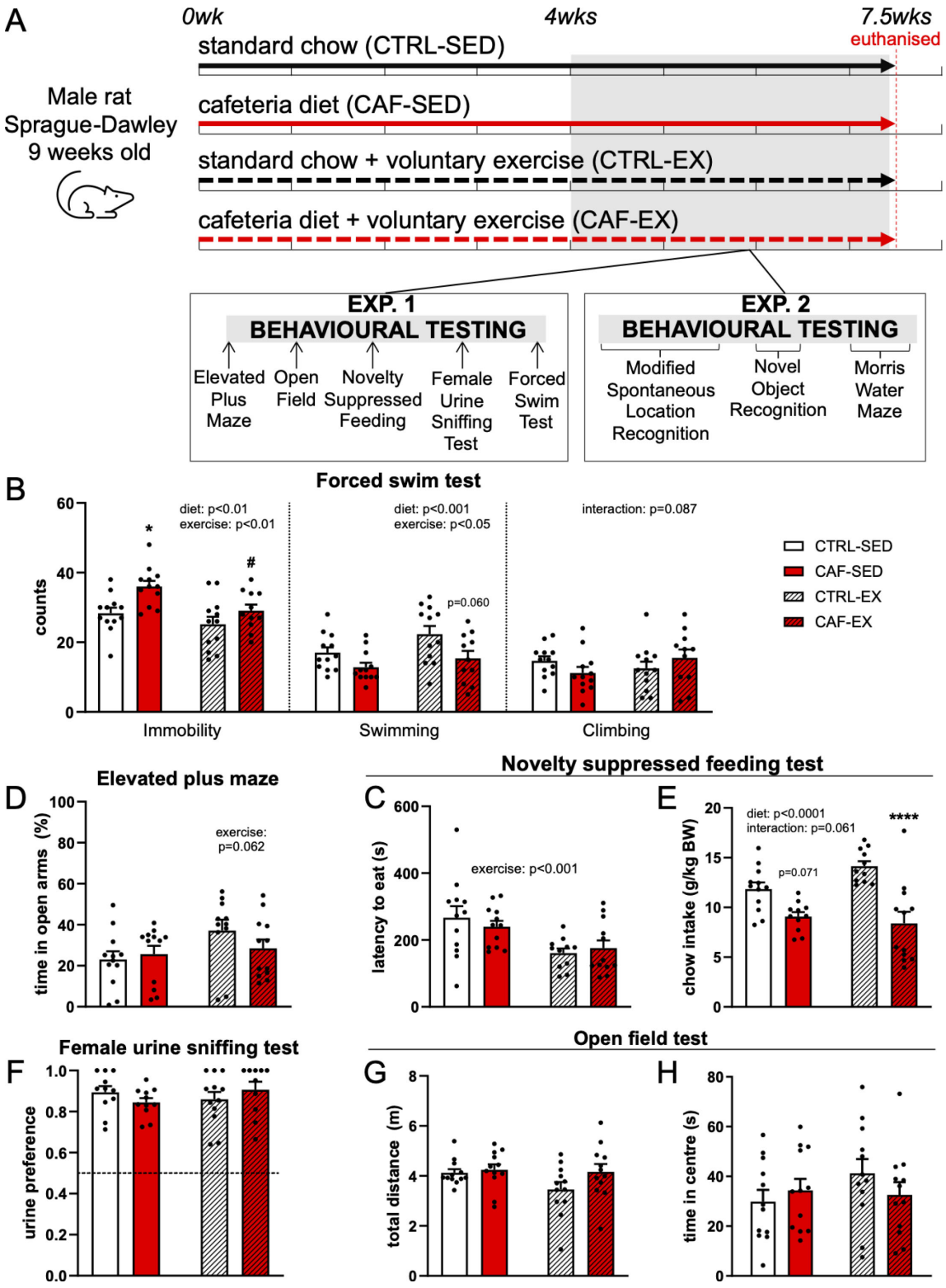

Figure 1. Exercise mitigated a cafeteria diet–induced increase in immobility in the forced swim test and exerted a modest anxiolytic effect irrespective of diet. (A) Experimental design. (B) Immobility: main effect of diet [$F(1,43) = 10.41$, $p < 0.01$] exercise [$F(1,43) = 7.87$, $p < 0.01$]; Swimming: main effects of diet [$F(1,43) = 8.80$, $p < 0.001$] and exercise [$F(1,43) = 4.39$, $p < 0.05$]; Climbing scores in the FST (n = 11–12). (C) Percentage of total time spent in EPM open arms (n = 11–12); effect of exercise [$F(1,43) = 3.69$, $p = 0.062$]; (D) Latency (s) to eat standard chow pellet in the NSF test arena (n = 11-12); Main effect of exercise [$F(1,43) = 12.48$, $p < 0.001$]; (E) Body weight–adjusted standard chow consumption (g) during NSF 30 min posttesting phase (n = 11–12); Main effect of diet [$F(1,42) = 30.14$, $p < 0.0001$], diet-exercise interaction [$F(1,42) = 3.70$, $p = 0.061$]; (F) Urine preference as time spent sniffing urine/total sniffing time in the FUST (n = 10–12). (G) Total distance travelled (m) in the OFT (n = 12). (H) Total time (s) spent in the center area of the OFT arena (n = 12). Data are expressed as mean ± SEM, $p = 0.071$, $^{*}p < 0.05$ and $^{****}p < 0.0001$ versus corresponding standard chow-fed group; $p = 0.060$, $p = 0.058$, $p = 0.056$ and $^{\#}p < 0.05$ versus corresponding sedentary group.

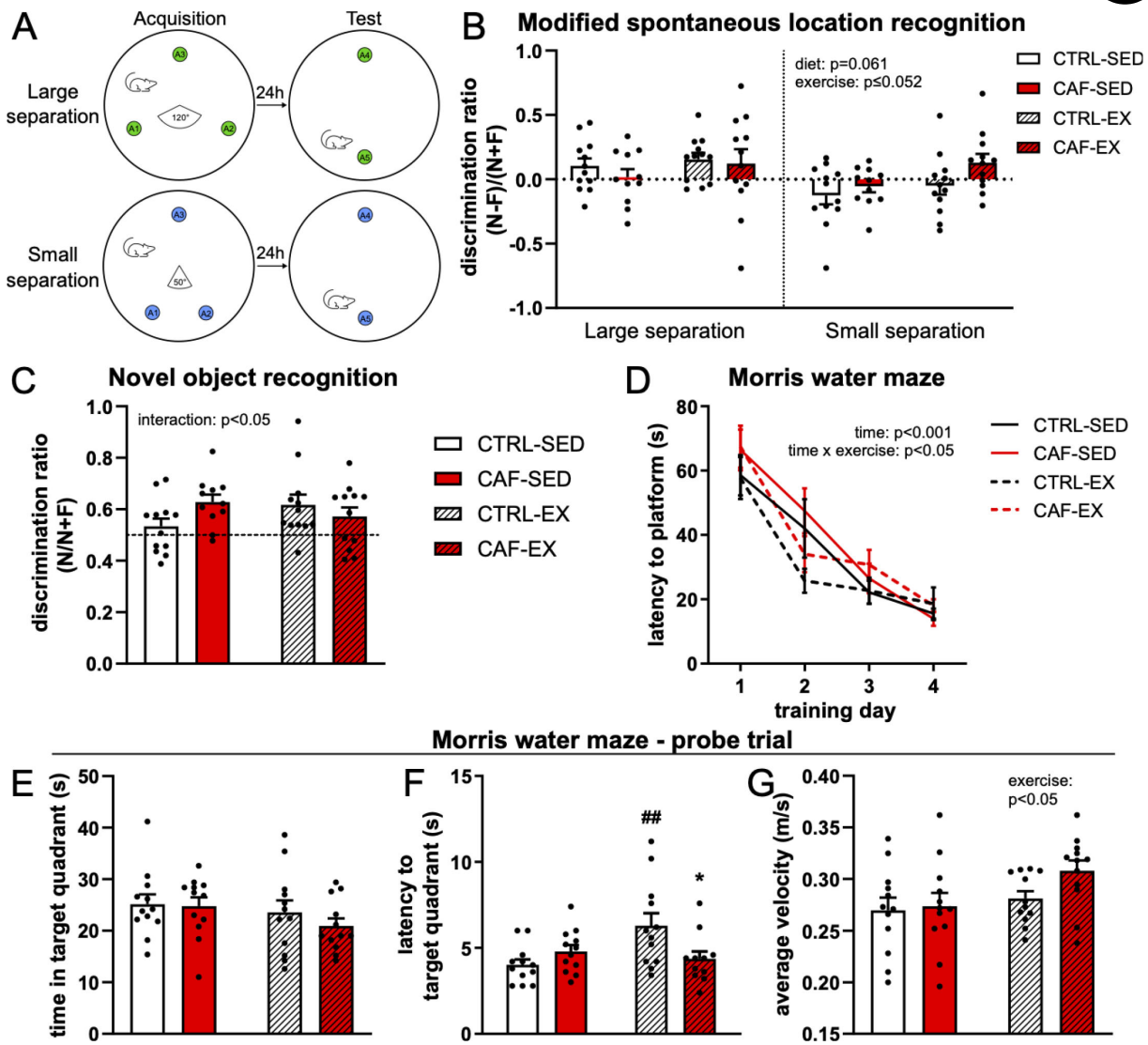

Figure 2. There was a modest effect of exercise but not a cafeteria diet on spatial learning and memory. (A) Schematics of the large and small separation in the MSLR task. (B) Discrimination ratio in the large and small separation of the MSLR ((novel (N) + familiar (F))/(N-F), n = 12). Small separation effect of diet [$F(1,43) = 3.69$, $p = 0.061$] and exercise [$F(1,43) = 3.98$, $p = 0.052$]; (C) Discrimination ratio in the NOR task (N/(N + F), n = 12), diet-exercise interaction [$F(1,43) = 4.17$, $p < 0.05$; (D, E). Average latency (s) to find the platform in the MWM, on (D) all training days; time [$F(3,24) = 54.88$, $p < 0.001$] and time-exercise interaction [$F(3,24) = 3.80$, $p < 0.05$]; (E) Cumulative time (s) spent in the target quadrant during the probe trial (n = 12). (F) Average latency (s) to reach the target quadrant during the probe trial (n = 11–12); [$H(3) = 8.25$, $p < 0.05$] ; (G) Average swimming velocity during the probe trial (n = 12), effect of exercise [$F(1,44) = 4.51$, $p < 0.05$]. Data are expressed as mean ± SEM, $^{*}p < 0.05$ versus corresponding standard chow-fed group; $p = 0.074$, $^{\#\#}p < 0.01$ versus corresponding sedentary group.

of 62/175 metabolites (Figure 5D). Conversely, exercise compared to sedentary controls induced differential expression of 5/175 metabolites in standard chow-fed animals (Figure 5E), and 4/175 metabolites in cafeteria diet–fed animals (Figure 5F). Supplemental Table S2 provides a complete list of quantified features.

Three of the top differentially abundant metabolites were notably affected by diet, exercise, and their interaction (Figure 5G–I). Cafeteria diet decreased the abundance of the dipeptide anserine (Figure 5G), the indole derivative indole-3-carboxylate (Figure 5H), and the nucleoside deoxyinosine (Figure 5I) in both sedentary (all FDR < 0.0001) and exercising animals (FDR < $0.0001_{[\text{anserine}]}$; FDR < $0.01_{[\text{indole-3-carboxylate}]}$; FDR < $0.05_{[\text{deoxyinosine}]}$). Interestingly, however, for all three metabolites, exercise attenuated the cafeteria diet–related downregulation (FDR < $0.0001_{[\text{anserine}]}$; FDR < $0.05_{[\text{indole-3-carboxylate \& deoxyinosine}]}$).

The effect of cafeteria diet on the caecal metabolome mainly involved amino acid metabolism and tRNA biosynthesis, as suggested by pathway enrichment analysis (Supplementary Table S3). Branched-chain amino acid (BCAA), phenylalanine, and tryptophan biosynthesis were all affected by diet in both sedentary and exercising animals. The tryptophan metabolite kynurenine was increased following cafeteria diet but only in sedentary animals (FDR < 0.05), while kynurenic acid was increased in both sedentary (FDR < 0.01) and exercising (FDR < 0.05) animals. Similarly, cafeteria diet increased serotonin, 5-hydroxyindole-3-acetic acid, and n-acetyl-5-hydroxytryptamine in sedentary (all FDR < 0.0001) and exercising animals (FDR < $0.0001_{[\text{n-acetyl-5-hydroxytryptamine \& serotonin}]}$; FDR < $0.001_{[\text{5-hydroxyindole-3-acetic acid}]}$), while kynurenine was increased with exercise but only in standard chow-fed animals (FDR < 0.05) (Supplementary Table S2).

Exercise had more limited effects on the metabolome independent of diet. Moreover, we found no pathway enrichment among nominally significant features. Beyond the top three features mentioned earlier (Figure 5G–I), the abundance of the nucleotide CMP (cytidine

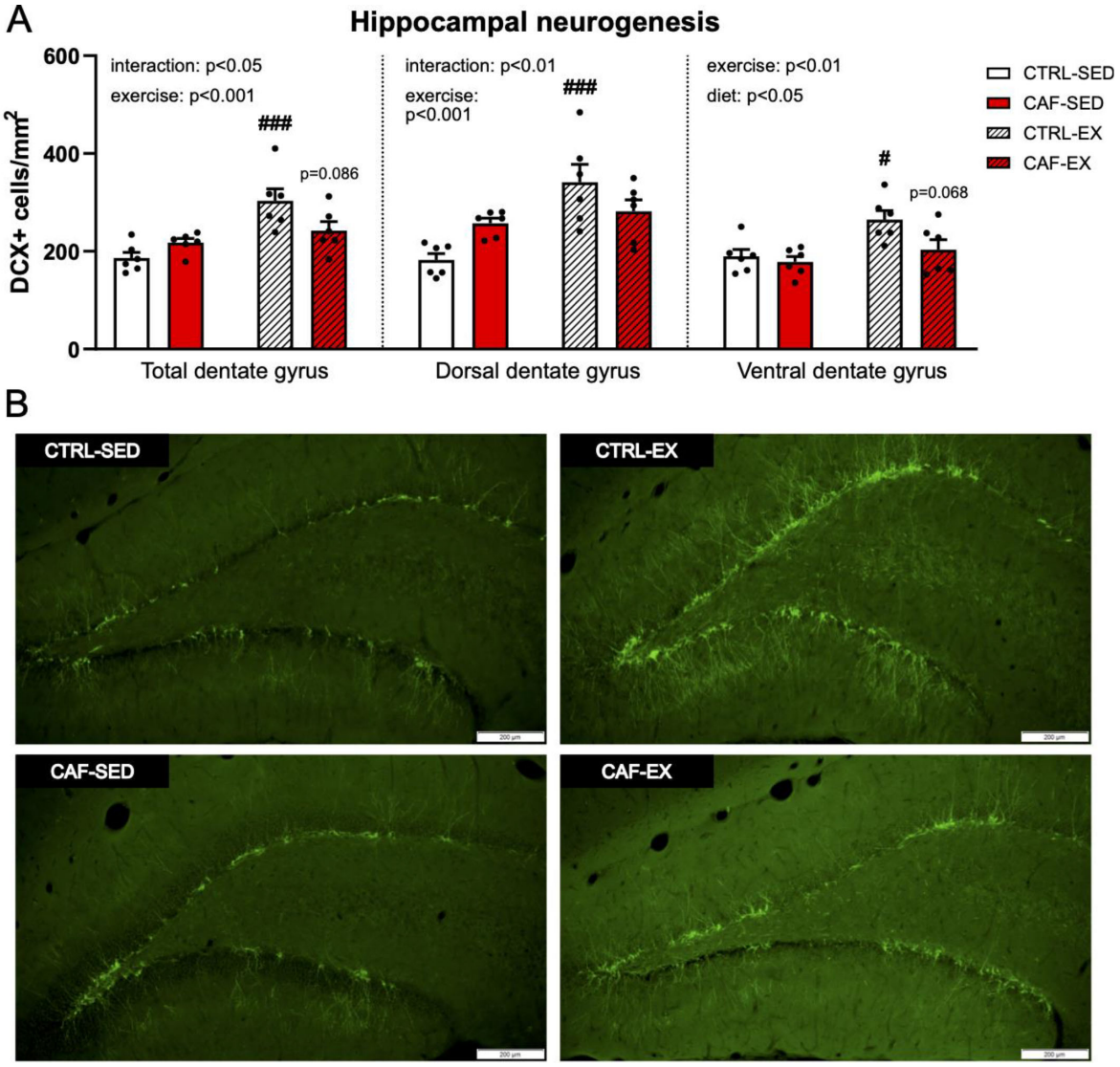

Figure 3. An exercise-induced increase in AHN is reduced by cafeteria diet. (A) Immature neurons in the DG (DCX^+ cells/mm^2, n = 6). Left panel: Total DG effect of exercise [$F(1,20) = 17.48$, $p < 0.001$] and diet-exercise interaction [$F(1,20) = 7.39$, $p < 0.05$]; middle panel: dorsal DG, effect of exercise [$F(1,20) = 15.33$, $p < 0.001$] and diet-exercise interaction [$F(1,20) = 8.28$, $p < 0.01$]; right panel: ventral DG, effect of diet [$F(1,20) = 4.98$, $p < 0.05$] and exercise [$F(1,20) = 9.29$, $p < 0.01$]. (B) Representative images of DCX^+ DG neurons taken at 10x magnification. Data are expressed as mean ± SEM, $p = 0.086$ and $p = 0.068$ versus corresponding standard chow-fed group; $^{\#}p < 0.05$ and $^{\#\#\#}p < 0.001$ versus corresponding sedentary group.

monophosphate) was decreased by exercise independent of diet (FDR < 0.01; Supplementary Table S2). Only three other metabolites were differentially abundant as an effect of exercise in chow-fed animals. The amino acid catabolite 2/3-hydroxybutyric acid was decreased by exercise (FDR < 0.05). Interestingly, it was also strongly decreased by cafeteria diet in both sedentary (FDR < 0.0001) and exercising (FDR < 0.01) animals, possibly related to BCAA metabolism. Finally, the B vitamin pantothenic acid and amino sugar n-acetylneuraminic acid were both increased by exercise (all FDR < 0.05).

Caecal metabolites independently correlate with behavior

To examine whether variations in individual caecal metabolites were associated with behavior, we carried out correlations between all caecal metabolomic features and behavioral task outcome measures.

In general, caecal metabolites were most strongly correlated with immobility time in the FST and the discrimination ratio in the MSLR (Supplementary Table S4). Focusing on the top associations for each readout (Figure 6A–E), we found a positive relationship between caecal cytosine levels and FST immobility score ($\rho = 0.74$, $p < 0.001$) (Figure 6A). Conversely, we found significant negative relationships between discrimination ratio in the large separation of the MSLR and caecal levels of 2-aminopimelic acid (more commonly known as aminoadipic acid) ($\rho = -0.66$, $p < 0.01$) (Figure 6B), 1-Phenylethyl acetate ($\rho = -0.68$, $p < 0.01$) (Figure 6C), 4-Vinylguaiacol ($\rho = -0.66$, $p < 0.01$) (Figure 6D), and the serotonin metabolite 5-Hydroxyindole-3-acetic acid ($\rho = -0.64$, $p < 0.01$) (Figure 6E). Some of these caecal metabolites were upregulated by cafeteria diet (Supplementary Table S2).

Discussion

In this study, we found that exercise attenuated cafeteria diet–induced increased immobility in the FST, suggesting that exercise exerted antidepressant-like effects in cafeteria diet–fed animals. Exercise had modest anxiolytic effects and exerted mild improvements in spatial learning in the MWM independent of the dietary intervention, while the cafeteria diet blunted the exercise-induced increase in AHN. In the plasma, exercise attenuated an increase in insulin and leptin resulting from cafeteria diet consumption, and both interventions differentially influenced concentrations of other plasma metabolic hormones. At the level of the

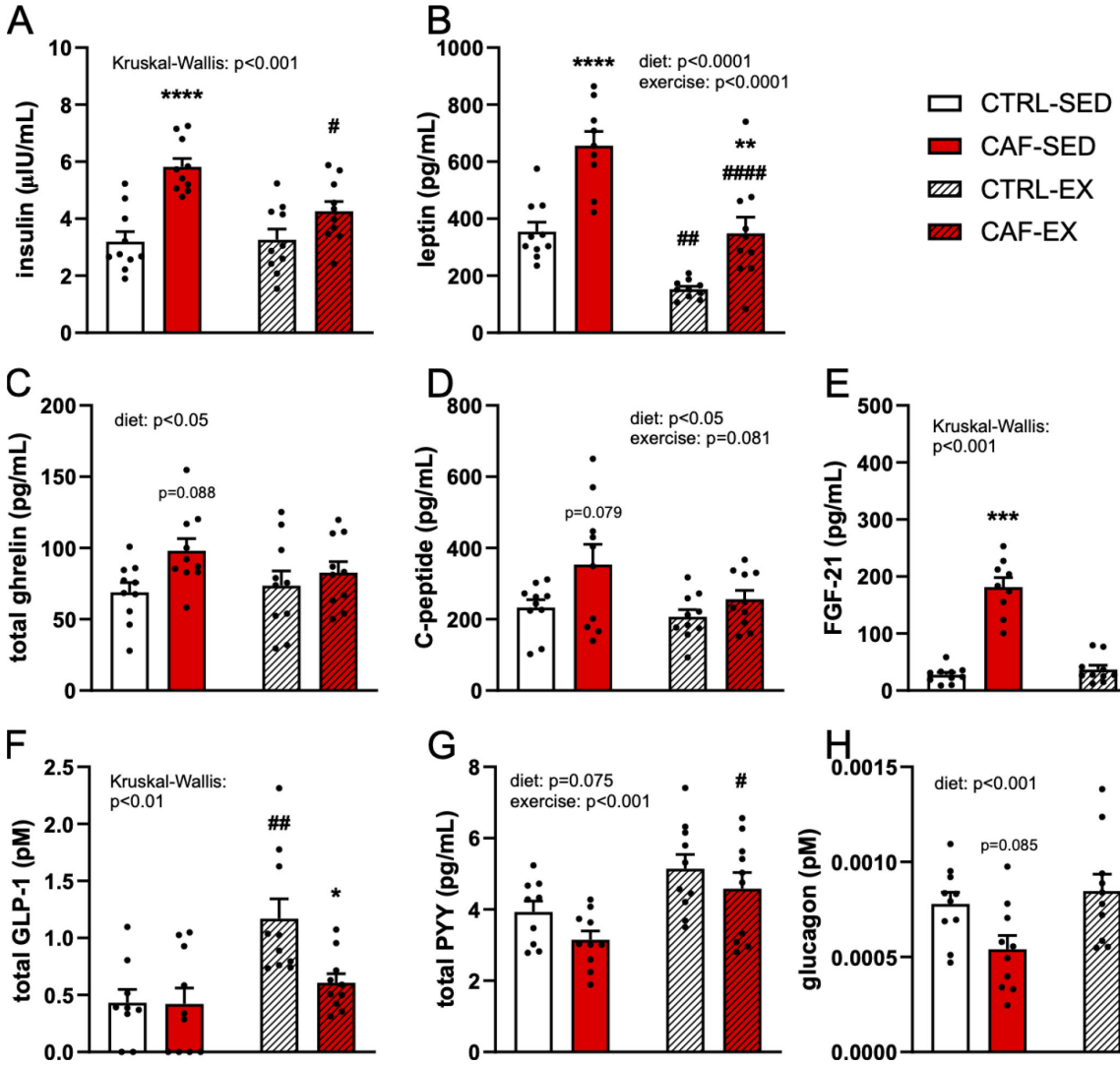

Figure 4. Exercise attenuated a cafeteria diet–induced increase in the metabolic hormones insulin and leptin in plasma. Plasma metabolic hormone concentrations (n = 9–10): (A) insulin (µIU/mL) [H(3) = 18.99, $p < 0.001$], (B) leptin (pg/mL), diet [F(1,35) = 36.11, $p < 0.0001$], exercise [F(1,35) = 38.01, $p < 0.0001$], (C) total ghrelin (pg/mL), diet [F(1,36) = 5.11, $p < 0.05$], (D) C-peptide (pg/mL) diet [F(1,36) = 6.15, $p < 0.05$] and exercise [F(1,36) = 3.22, $p = 0.081$], (E) FGF-21 (pg/mL) [H(3) = 25.51, $p < 0.001$], (F) total GLP-1 (pM) [H(3) = 12.61, $p < 0.01$], (G) total PYY (pg/mL) diet [F(1,35) = 3.36, $p = 0.075$] and exercise [F(1,35) = 13.24, $p < 0.001$] and (H) glucagon (pM), diet [F(1,36) = 18.09, $p < 0.001$]. Data are expressed as mean ± SEM, $p = 0.088$, $p = 0.085$, $p = 0.079$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ and $^{****}p < 0.0001$ versus corresponding standard chow-fed group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ and $^{\#\#\#\#}p < 0.0001$ versus corresponding sedentary group.

caecal metabolome, exercise had few effects but attenuated a cafeteria diet–induced reduction in the abundance of anserine, indole-3-carboxylate, and deoxyinosine. While these effects were not independently associated with behaviors, several other caecal metabolites displayed robust relationships with cognition- and mood-related tasks.

Our findings suggest that the cafeteria diet increased despair-like behaviors as observed by increased immobility in the FST. Previous studies using hypercaloric (normal chow + industrialized animal lard and corn oil) (55) or high-fat diets (56) have yielded varying results in the FST, indicating that the exact diet formulation may play a role. While we did not observe effects of exercise alone on behavior in the FST, in accordance with prior literature (37, 57–59), when rats consumed a cafeteria diet, exercise attenuated immobility in the FST suggesting an antidepressant-like effect. Comparable reductions in FST immobility have been reported following 6–10 weeks treadmill exercise interventions in rodents fed high-fat diets for 20–22 weeks (60, 61). Interestingly, caecal levels of the nucleotide cytosine were positively associated with residualized immobility score in the FST. Administration of cytidine (the nucleoside form of cytosine) has previously been found to decrease immobility time in the FST (62). This apparent discrepancy may be due to enzymatic metabolism of cytosine to cytidine (63), possibly by gut microbes, accounting for this inverse relationship with FST behavior. While cytidine was detected in our dataset, it did not correlate with FST immobility score, nor did other pyrimidines or their derivatives (data not shown). Thus, the possible role of gut microbiota in mediating a relationship between nucleic acids and mood-related outcomes warrants further study.

Caecal metabolome analysis showed that cafeteria diet increased tryptophan, serotonin, kynurenine, kynurenic acid and 4,8-dihydroxyquinoline-2-carboxylic acid (xanthurenic acid), suggesting enhanced peripheral conversion of tryptophan into metabolites that cannot cross the blood–brain barrier. This likely reduces the availability of tryptophan in the brain for local serotonin production (64). A previous study showed that a 4-week cafeteria diet affects 5HT1A receptor expression in the hippocampus, suggesting an effect of cafeteria diet on serotonin

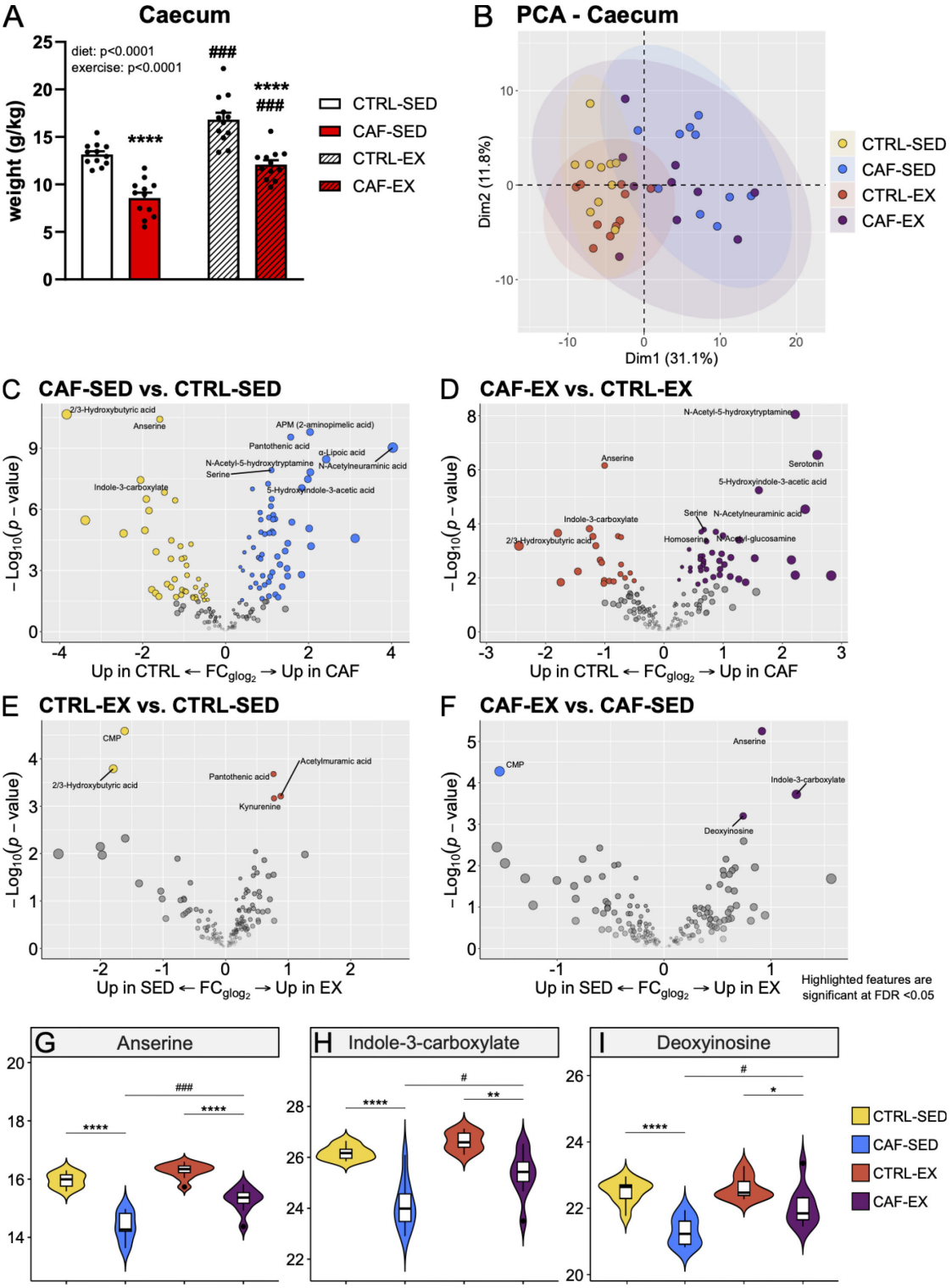

Figure 5. Exercise attenuated a cafeteria diet–induced decrease in caecal metabolites anserine, indole-3-carboxylate, and deoxyinosine. (A) Effects of cafeteria diet and exercise on body weight–adjusted caecum weight (g/kg, n = 12), effect of diet [F(1,44) = 73.80, $p < 0.0001$] and exercise [F(1,44) = 43.98, $p < 0.0001$], Data are expressed as mean ± SEM, $^{****}p < 0.0001$ versus corresponding standard chow-fed group; $^{###}p < 0.001$ versus corresponding sedentary group. (B) Principal component analysis (PCA) with 95% concentration ellipses showing effects of cafeteria diet and exercise on caecal metabolomes (n = 10). (C–F) Volcano plots of quantified caecal metabolites (n = 175 features), comparing (C) cafeteria diet (CAF) versus standard chow (CTRL) in sedentary (SED) animals, (D) CAF versus CTRL in exercising (EX) animals, (E) EX versus SED in CTRL-fed animals, and (F) EX versus SED in CAF-fed animals. Highlighted features represent upregulated metabolites (p-value adjusted for false discovery rate (FDR) < 0.05). (G–I) Violin and box- and whisker plot (median represented by horizontal line) of the normalized peak area of caecal metabolites (G) anserine, (H) indole-3-carboxylate, and (I) deoxyinosine (all n = 10, FDR-adjusted p-values; $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{****}p < 0.0001$ versus corresponding standard chow-fed group; $p = 0.094$, $^{\#}p < 0.05$, and $^{###}p < 0.001$ versus corresponding sedentary group). Full list of quantified metabolites available in Supplemental Table S2. Abbreviations: fold change (FC), generalized logarithm base 2 ($glog_2$).

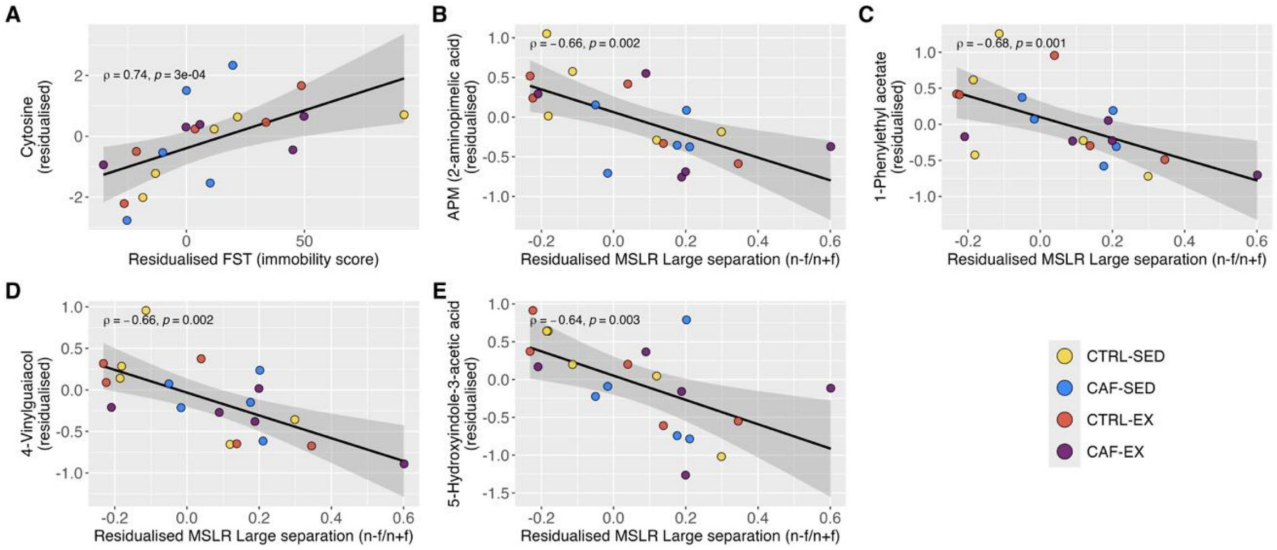

Figure 6. Caecal metabolites independently correlate with behavior. (A–E) Spearman correlations between residualised caecal metabolite abundance (vertical axes) and behavioral readouts (horizontal axes) significant at the FDR < 0.1 level. (A) Caecal cytosine and forced swim test (FST) immobility score. (B) Caecal 2-aminopimelic acid (also known as aminoadipic acid) and discrimination ratio in the large separation of the MSLR. (C) Caecal 1-Phenylethyl acetate and discrimination ratio in the large separation of the MSLR. (D) Caecal 4-Vinylguaiacol and discrimination ratio in the large separation of the MSLR. (E) Caecal 5-Hydroxyindole-3-acetic acid and discrimination ratio in the large separation of the MSLR. Data are expressed as model residuals at the original scales (either normalized peak areas for caecal metabolites or stated units for behavioral readouts) after regressing out the effect of experimental condition using linear regression. Spearman's rho and nominal *p*-value are stated for each association.

signaling (65). Our analysis revealed that caecal 5-hydroxyindole-3-acetic acid, the main metabolite of serotonin, negatively associated with discrimination ratio in the MSLR independently of experimental condition, but its abundance also increased with cafeteria diet. Aminoadipic acid displayed the same relationship with discrimination ratio and cafeteria diet. Produced peripherally as part of lysine catabolism, aminoadipic acid is a substrate of kynurenine aminotransferase, which catalyzes the conversion of kynurenine to kynurenic acid (66). Intrahippocampal aminoadipic acid administration decreases endogenous kynurenine levels in rats (66), and aminoadipic acid along with BCAA concentrations are increased in plasma of prediabetic, insulin-resistant rats (67). Furthermore, kynurenine metabolites negatively associate with cognitive impairment in middle-aged prediabetic and type-2 diabetic patients (68). In our study, lysine and BCAA metabolism were increased by cafeteria diet, suggesting a greater presence of precursors of aminoadipic acid. We speculate that the metabolic state associated with a cafeteria diet alters tryptophan and kynurenine metabolism dynamics, making them less available centrally and contributing to memory deficits. However, to what extent these changes affect serotonin production in the brain remains to be elucidated. While treadmill exercise increases serotonin production in the dorsal raphe nucleus in rats (69), supporting an antidepressant-like effect, further investigation is needed to understand the complex interactions between a cafeteria diet and exercise on tryptophan and serotonin metabolism. Finally, two metabolites of exogenous origin, 4-Vinylguaiacol (70) and 1-Phenylethyl acetate (71), correlated with MSLR discrimination ratio. As these metabolites are used industrially as flavoring agents, the source of exposure is likely from the cafeteria diet. The link to episodic memory is not immediately obvious, and these correlations may instead reflect variations in metabolism that depend on individual physiological factors such as cardiorespiratory fitness, lean body mass, and gut microbiota composition (72), rather than a direct causal relationship with memory performance.

The cafeteria diet did not induce an anxiety-like phenotype in the EPM, NSF test, and OFT. Similarly, a study in male Wistar rats found no effects of a 10-week cafeteria diet on anxiety-like behavior in the EPM (73). Voluntary wheel running decreased the latency to eat in the NSF test, and showed a tendency to increase the time spent in the open arms of the EPM by standard-chow-fed animals, indicating a potential anxiolytic effect of exercise which affirms previous findings in male rodents (14, 37, 58).

We found that pattern separation (large and small configuration) was not altered by the cafeteria diet, despite a previous study describing that a transgenerational cafeteria diet (eight generations) decreased pattern separation (medium configuration) using touchscreen operant chambers (74). This suggests that long-term dietary exposure may be necessary for cognitive deficits to emerge. Short-term recognition memory has been reported to be impaired by a 6-week cafeteria diet (75), which we did not observe in the NOR in this study. Previous studies similarly report spatial learning and memory impairments in the MWM due to a cafeteria diet (26, 76), but we did not replicate these findings. It is important to note that in these studies, rats also had access to 10% sucrose solutions or soft drinks alongside the diet, whereas in the current study rats had access to water only. Moreover, previous studies comparing the effects of exercise or a high-fat (but not high-sugar) diet on behavior in MWM reported that spatial learning and memory alterations were observed only when interventions began in adolescence and not adulthood (77, 78). This suggests that adult rodents are more resistant to diet and exercise interventions than their younger counterparts (16, 78). However, analysis of search strategies employed by the adult rats in the current study revealed that exercise mitigated a decrease in circling behavior in rats with access to the cafeteria diet. Interestingly, employment of spatially imprecise search strategies has been shown to be related to age and neurogenic capacity (79). While we did not observe effects of a cafeteria diet alone on AHN, exercise increased hippocampal DCX^+ neuron density in chow-fed animals in line with previous reports (29, 37). The cafeteria diet blunted this pro-neurogenic effect of exercise. As previously reported, a cafeteria diet provided to rats from adolescence decreased AHN (26), and treadmill exercise during adolescence mitigated a high fat diet–induced decrease in AHN (77), suggesting that a cafeteria diet and/or exercise during adolescence rather than in adulthood may have a greater impact on AHN.

In agreement with previous literature (80–83), cafeteria diet–fed sedentary animals displayed elevated plasma insulin and leptin, which

were attenuated by exercise. Previous studies show that markers of insulin resistance were reversed by treadmill or swimming exercise in rats fed a high-fat/high-carbohydrate diet or cafeteria diet (84, 85). While leptin and insulin may promote AHN and cognitive behaviors (30, 51, 52), resistance to these hormones following prolonged elevation has been associated with depression-like behaviors and cognitive impairment (52, 86). Leptin and hippocampal insulin resistance have been shown to increase immobility in the FST (87, 88) and worsen spatial learning in the MWM (84). Therefore, attenuation of cafeteria diet–induced increases in insulin and leptin by exercise may have contributed to the mitigating effects of exercise on cafeteria diet–induced immobility in the FST in the current study. This hormonal normalization likely resulted from exercise-induced decreases in adipose tissue, given that white adipose tissue releases leptin and regulates insulin sensitivity (89, 90). The cafeteria diet did not decrease tGLP-1 in sedentary animals, which contrasts with a previous study (91), potentially due to differences in dietary intervention duration. However, exercise increased plasma tGLP-1 concentrations, mirroring observations in human studies (92, 93), but this was blunted in rats fed a cafeteria diet. Activation of the GLP-1 receptor via exendin-4 has been shown to enhance AHN (33). Thus, it is possible that attenuation of the exercise-induced increase in AHN by a cafeteria diet observed here may be mediated by circulating concentrations of tGLP-1. Exercise also increased plasma PYY concentrations consistent with human studies (94, 95). Increased anxiety-like behaviors in the EPM and immobility in the FST were previously reported in PYY knockout mice (96), and centrally administered PYY decreased anxiety-like behaviors in the EPM (97). Therefore, the exercise-induced increase in PYY in the cafeteria-diet fed animals potentially contributed to its anxiolytic effects observed here.

Studies show that metabolic dysregulation is accompanied by shifts in gut microbiota (98, 99) like increased taxa related to fat deposition (99) and obesity (98, 100). Microbial metabolism is largely determined by gut microbial composition and indeed we found that caecal metabolite abundance was significantly altered by cafeteria diet and attenuated by exercise. Exercise attenuated a cafeteria diet–induced decrease in caecal abundance of the metabolite anserine, a histidine-containing dipeptide which is deficient in aged mice and associated with depression-like behaviors (101). Supplementation with anserine in combination with other dipeptides is associated with a reduction in depression scores (102) and improved cognitive function in humans (103, 104) and improved hippocampal integrity in mice (105). Exercise also attenuated a cafeteria diet–induced decrease in caecal deoxyinosine and indole-3-carboxylate. Interestingly, hippocampal deoxyinosine was reportedly decreased in a mouse model of depression (106), whereas chronic variable stress increased urine concentrations of indole-3-carboxylate (107). Indole-3-carboxylate is biochemically related to tryptophan, a precursor of serotonin, which is negatively correlated with depression scores (108, 109). However, these three metabolites were not associated with behavior independently of diet and exercise in our study. Instead, their regulation may be related to chow/cafeteria diet consumption, since they are food-derived as annotated by the human metabolome database (110).

Taken together, exercise attenuated depression-like behaviours and an increase in plasma concentrations of insulin and leptin in rats fed a cafeteria diet. This was coupled with an exercise-induced attenuation of a reduced abundance of caecal metabolites anserine, deoxyinosine and indole-3-carboxylate due to the cafeteria diet. These circulating hormones and caecal metabolites may be instrumental in mediating the interaction between the effects of a cafeteria diet and exercise on depression-like behaviour. Interestingly, we found that a standard healthy diet is necessary for exercise to increase AHN. These results suggest that dietary quality may determine whether exercise can enhance hippocampal neurogenesis. Finally, the findings provide insight into potential gut-mediated mechanisms and the involvement of circulating metabolic hormones underlying the effects of a cafeteria diet and exercise on hippocampal function. This has important implications for the development of lifestyle interventions targeting mood and cognition.

Methods

Animals

Male Sprague-Dawley rats obtained from Envigo Laboratories (United Kingdom) at approximately 7 weeks old (225–250 g) were housed in groups of four in standard conditions (22 ± 1°C, 50% relative humidity) on a 12-h light-dark cycle (lights on at 7:00 a.m.), with *ad libitum* access to food and water. At the start of the experiment, at approximately 9 weeks old, animals were pair-housed for the duration of the study. All animal procedures were performed under licenses issued by the Health Products Regulatory Authority (AE19130/P123, HPRA, Ireland), in accordance with the European Communities Council Directive (2010/63/EU) and approved by the Animal Experimentation Ethics Committee of University College Cork (2019/025).

Experimental design

At pair-housing, animals were randomly divided into four experimental groups; sedentary animals with access to standard chow (CTRL-SED, n = 12), sedentary animals with access to cafeteria diet (CAF-SED, n = 12), animals with voluntary access to running wheels and standard chow (CTRL-EX, n = 12), and animals with voluntary access to running wheels and cafeteria diet (CAF-EX, n = 12, Figure 1A). Standard chow (Envigo, UK) consisted of 6.2% fat (of which 0% saturated fat), 44.2% carbohydrates (of which 0% sugar), 18.6% protein, and 3.5% fibre (Supplementary Table S1). The cafeteria diet consisted of several different food items high in fat and/or sugar, with two high-fat and two high-sugar items given each day in rotation in addition to standard chow, for the duration of the experiment (7.5 weeks), as previously described (111) (Supplementary Table S1). All food was provided in excess, *ad libitum*. Exercising animals had continuous access to a running wheel (Techniplast, UK) for the duration of the experiment. Running distance (km) was recorded in 24 h increments. Weight gain was calculated as % weight gain $= \frac{\text{end weight} - \text{starting weight}}{\text{starting weight}} \times 100$. Weights were not significantly different between groups at the start of the experiment.

Four weeks following intervention onset, anxiety-like behavior was assessed in the EPM, NSF test, and OFT, anhedonia in the female urine sniffing test (FUST), and antidepressant-like behavior in the FST (Figure 1A). In a second cohort of rats randomly allocated to the same experimental groups (CTRL-SED, n = 12; CAF-SED, n = 12; CTRL-EX, n = 12; CAF-EX, n = 12), pattern separation, recognition memory, and spatial learning and memory were assessed in the MSLR, NOR and MWM tests, respectively (Figure 1A), 4 weeks following intervention onset.

Behavioral testing

Elevated plus maze Anxiety-like behavior was assessed in the EPM (112). Animals were habituated to a dimly lit (red light, ±5 lux) room 1 h prior to testing. The maze consisted of two opposed open (50 × 10 cm) and two opposed closed (50 × 10 cm, 40 cm walls) arms mounted at 90° angles facing a central platform (10 × 10 cm), elevated 50 cm above the floor. Each animal was placed on the central platform facing an open arm and left to explore freely for 5 min, then returned to its home cage. Behavior was monitored and video tracked. The maze was cleaned using 70% ethanol between each animal to eliminate olfactory cues. Time spent in open arms was scored manually, blinded to experimental groups. Arm entries were recorded when all paws of the animal crossed an arm border. Data are presented as the percentage of total test time in open arms.

Novelty suppressed feeding The NSF test was used to measure anxiety-like behavior (37). The day before the test (6 p.m.), all food was removed from the home cage. Animals were food-deprived for no more than 16 h. The day of the test, animals were habituated to the experimental room for 1 h and then placed in a brightly lit (±1000 lux) circular arena (90 cm diameter) with bedding. A food pellet was placed on a white plastic base in the centre. Latency (s) to begin eating was recorded during 10 min. Once the rat began eating, or the 10-min time limit was reached, the rat was removed from the arena and returned to its home cage with access to preweighed standard chow. After 30 min, chow was removed and weighed to determine the amount consumed adjusted to body weight (g/kg). The arena and food platform were cleaned using 70% ethanol between each animal to eliminate olfactory cues.

Female urine sniffing test Anhedonia was measured using the FUST according to (113). Urine was collected from adult female Sprague-Dawley rats in oestrous. Oestrous cycle was determined by observing vaginal secretion (collected with a plastic transfer pipette, tip diameter < 1 mm) under a light microscope.

Experimental male animals were habituated to the testing room for 15 min, then to a clean, dry cotton bud inside the cage for 45 min. The cotton bud was removed and replaced with a new cotton bud with dH_2O for 3 min, which was again removed. After 45 min, each animal was exposed to another cotton bud with female oestrus urine for 3 min. Each exposure was recorded by video camera. Time spent sniffing the cotton buds was scored manually, blinded to experimental groups. Preference to sniff urine compared to water was calculated as $\text{urine preference} = \frac{\text{time spent sniffing urine}}{\text{time spent sniffing urine} + \text{water}}$.

Forced swim test The modified FST was used to measure antidepressant-like behavior (114). In the preswim, rats were individually exposed to a water tank for 15 min (21 cm diameter, filled to 30 cm with 23–25°C water). Twenty-four hours later, rats were placed back in the water tank for 5 min. Behavior during the 5 min test was video recorded. Following testing, rats were removed from the tank, gently towel-dried and returned to their home cage. Active (climbing and swimming) and passive (immobility) behaviors during the test were scored manually, blinded to experimental groups, in 5 s bins as previously described (50).

Open field General locomotor activity was assessed in the OFT. Animals were habituated to the testing room for 1 h before testing. Animals were placed in a brightly lit (±1000 lux) circular arena (90 cm diameter), allowed to explore for 10 min, and returned to their home cage. Distance moved (m) and time in centre (s) were analyzed using Noldus EthoVision XT 11.5 tracking software. Centre area diameter was set at 45 cm according to (115). The arena was cleaned using 70% ethanol between each animal exposure to eliminate olfactory cues.

Modified spontaneous location recognition test Pattern separation, the ability to discriminate between highly similar memories which is associated with AHN, was assessed in the MSLR test according to (115). Animals were habituated to a dimly lit circular arena (~20 lux, 90 cm diameter) with bedding for 10 min per day for 5 consecutive days prior to testing. External cues were placed in the testing room for spatial navigation. Following habituation, during acquisition, animals were allowed to explore three identical objects (33 cl glass beer bottles, or soda cans) for 10 min, once for the large separation (LS) and once for the small separation (SS) test. For LS, the objects were separated by 120° (Figure 2A). For SS, two of the objects (A1 and A2) were separated by 50° with the third object (A3) at an equal distance between them (Figure 2A). Twenty-four hours after acquisition, animals were allowed to explore two of the objects from the acquisition phase for 5 min. The familiar (A4) was placed in the same location as A3, while the novel (A5) was placed between the locations of A1 and A2 (Figure 2A). Separation order, object type, and object location were randomized across tests. Behavior was recorded and videos were analyzed blinded to experimental groups to determine exploration time with novel and familiar objects. The discrimination ratio (DR) was calculated as $\text{DR} = \frac{(\text{time exploring novel object} - \text{familiar object})}{(\text{time exploring novel object} + \text{familiar object})}$. Objects were cleaned using 70% ethanol between each animal to eliminate olfactory cues.

Novel object recognition Recognition memory was measured in the NOR test. Animals were habituated to a dimly lit circular arena without bedding (~20 lux, 90 cm diameter) for 10 min. The next day, animals were allowed to explore two identical objects (ceramic mug, or 250 ml graduated borosilicate bottle) in the arena for 10 min. Twenty-four hours after acquisition, one object was replaced with a novel object (the object not used during acquisition), and animals were allowed to explore for 5 min. Behavior was recorded and videos were analyzed blinded to experimental groups to determine exploration time with novel and familiar objects in the 5 min test. The DR was calculated as $\text{DR} = \frac{\text{time exploring novel object}}{(\text{time exploring novel object} + \text{familiar object})}$. The arena and objects were cleaned using 70% ethanol between each animal to eliminate olfactory cues.

Morris water maze Hippocampal-dependent spatial learning and memory were assessed in the MWM as previously described (116). Animals were habituated to the room for 1 h before testing. A circular pool (180 cm diameter) was filled with water (22 ± 1°C). A transparent platform was placed 1–2 cm below the water surface at a fixed location in the north-west quadrant, 15 cm from the pool wall. External cues were placed in the testing room for spatial navigation. During training (days 1–4), animals were placed in the pool at one of four release points (NE, E, S, and SW), each point used once per day. Animals underwent four daily trials for 4 consecutive days. If the animal found the platform within 120 s, they were left on the platform for 10 s before continuing to the next trial. If the animal failed to reach the platform within 120 s, they were guided to the platform and remained there for 30 s before continuing to the next trial. Trials were recorded and analyzed using Noldus EthoVision XT 11.5 tracking software. On day 5 (probe trial), the platform was removed and animals allowed to explore the pool for 60 s starting at the SE point. Latency to enter and time spent in the platform quadrant (s), and average velocity were analyzed using Noldus EthoVision XT 11.5 tracking software to assess spatial memory. Learning performance and search strategies were assessed as described in Supplementary Methods.

Blood and tissue collection

One day after the last behavioral test, 1–3 h after cessation of the diet and exercise exposures, half of the animals per group (n = 6) were weighed and euthanized by rapid decapitation during the light cycle to collect fresh tissues. Trunk blood was collected in 3 mL EDTA-coated tubes (Vacuette, Greiner Bio-One) and centrifuged for 10 min (3220 x *g*, 4°C) to collect plasma, which was stored at –80°C until used for measurement of metabolic hormones (Supplementary Methods). eWAT and BAT were dissected and weighed. Whole caecum (n = 12) was collected and weighed. Caecum content (n = 10) was snap frozen using dry ice and stored at –80°C until preparation for metabolomic analysis (Supplementary Methods).

Half of the animals per group (n = 6) of the first cohort were weighed and transcardially perfused 1–3 h after cessation of the diet and exercise exposures to assess immature hippocampal neuron counts as a measure of AHN. Sodium pentobarbital (90 mg/kg) was injected intraperitoneally as anaesthetic overdose. Sufficient anesthesia depth was identified by loss of toe pinch reflex. Animals were pinned in a dorsal recumbent position and their thorax was opened to insert a catheter into the heart left ventricle. Ice-cold phosphate-buffered saline (PBS) was perfused by pump (35–40 mL/min) until efflux ran clear, followed by 4% paraformaldehyde (PFA) in PBS. During PBS perfusion, eWAT was dissected and weighed to determine adiposity. Whole brains were postfixed in 4% PFA in PBS for 24 h, transferred to 30% sucrose in PBS until fully sunken, snap frozen in isopentane using liquid nitrogen, and stored at − 80°C until sectioning. Brains were sectioned coronally at 40 μm using a Leica CM1950 cryostat, collected free-floating in a series of 12 in cryoprotectant (25% 0.1M PBS, 30% ethylene glycol, 25% glycerol, and 20% dH_2O) and stored at − 20°C until immunohistochemical staining.

Immunohistochemistry

For immunohistochemical staining of doublecortin (DCX, n = 6 per group), a marker of immature neurons, sections were washed in 0.1M PBS (3 × 5 min) and blocked with 10% donkey serum in 0.5% Triton X-100 in PBS (PBS-T) for 2 h at room temperature (RT). Sections were incubated in primary antibody (rabbit anti-DCX; Abcam, AB18723, 1:5000) for 48 h at 4°C. Antibodies were diluted in 5% donkey serum in 0.5% PBS-T. Sections were washed in 0.5% Tween in PBS (PBS-Tw, 3 × 20 min), incubated in secondary antibody (Alexa Fluor 488-conjugated donkey anti-rabbit, Invitrogen, AB21206, 1:500) for 2 h at RT and washed in PBS-Tw. Sections were incubated in 4′,6-diamidino-2-phenylindole (DAPI) (5 mg/mL, 1:50,000 in PBS) for 3 min, washed in PBS, mounted onto Superfrost Plus slides and cover-slipped using Dako fluorescent mounting media.

Microscopy and image analysis

The DG was imaged using an Olympus BX53 Upright Research Microscope at 20x magnification for DCX. DCX^+ cells were counted blinded to experimental groups in every 12th section using ImageJ. DG area (mm^2) was

measured using ImageJ on 10x magnification images of DAPI and cell counts were expressed as cells/mm^2. The dorsal hippocampus (dHi) was defined as anterior-posterior (AP): Bregma − 1.8 to − 5.2, and ventral hippocampus (vHi) as AP: − 5.2 to − 6.7 (112, 117, 118). Sections at AP − 5.2 were only considered vHI if ventral DG was clearly present at the bottom of the section (117). Note: in coronally sectioned rat brain, rostral sections typically only contain dHi, whereas caudal sections containing vHi may also contain portions of dHi and intermediate hippocampus (119, 120). Three dorsal and three ventral sections were analyzed, selecting sections of similar AP coordinates from Bregma for all animals where possible.

Bioinformatic analysis

Differential expression analyses were limited to non–drug-related features (metabolites) annotated at the highest confidence levels 1 and 2a (caecal features, n = 212) and performed in R (version 4.1.1). Raw feature peak area values below their associated detection limit (as reported by MS-Omics) were considered missing (i.e., set to "*NA*"); only features with maximum 25% missingness per condition were retained for quantification (features remaining, n = 201). To remove features displaying high technical variance, only metabolites with < 10% relative standard deviation in the pooled quality control samples were retained (features remaining, n = 175). Data were subsequently normalized with variance stabilising normalization (VSN), using the "*vsn*" package (allowing default 10% outliers). While originally developed for microarray data (121), VSN has successfully been applied in untargeted (122) and simulated (123) metabolomics of comparable dataset size to the one herein, capitalizing on similar mean-variance relationships (124) and error models (125). The generalized logarithm base 2 ($glog_2$) transformation employed in VSN approximates the standard log_2 function for values »0. The "*limma*" package was used for differential expression analysis, with trend = TRUE and robust = TRUE in the eBayes function (126). Resulting feature *p* values were adjusted for multiple comparisons with the Benjamini-Hochberg method, with a 5% FDR threshold for significance. Pathway over-representation analysis with nominally ($p < 0.05$) differentially abundant caecal metabolites was performed using MetaboAnalystR (v 4.0), with *Rattus norvegicus* Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and hypergeometric tests (127). For correlations between behavioral tasks (20 rats for each behavioral measure) and all caecal metabolomic features, the effect of experimental condition was first regressed out using linear models ("lmFit" in "*limma*" or "lm" in the "*stats*" R packages). Spearman correlations were performed with the "*Hmisc*" package in R. Resulting *p* values were then adjusted by FDR separately for each readout. Correlations were considered significant at the FDR < 0.1 level. For a complete list of R packages used in this study, see Supplementary Table S5.

Statistical analysis

Data were checked for outliers using the Grubbs outlier test, and for normality using Shapiro-Wilk. Identified outliers were removed from analyses. Except for running distance and MWM training, data were analyzed using two-way ANOVA in GraphPad Prism and SPSS. Running distance data were analyzed using two-way ANOVA with repeated measures, with post-hoc analysis comparing each week using Sidak's multiple comparisons test. MWM training outcomes were analyzed using two-way ANOVA with repeated measures, with post-hoc analysis on individual training days using two-way ANOVA and Tukey's multiple comparisons test. Post-hoc analyses of other two-way ANOVAs were performed using Tukey's multiple comparisons test. Non-normally distributed data were analyzed for differences in group distributions using Kruskal-Wallis with pairwise Mann-Whitney U post-hoc comparisons. Statistical significance was set at $p < 0.05$, with data presented as means ± standard error of the mean (SEM). For two-way ANOVA results, diet–exercise interactions are reported only when statistically significant.

Data availability

All data are available upon request.

Acknowledgments

The authors thank Dr. Anna Golubeva and Dr. Gerard Moloney for their technical assistance.

Author contributions

MHCN conducted and designed experiments, collected and analyzed the data, prepared the figures, acquired funding and wrote the manuscript. SN conducted and designed experiments, collected and analyzed the data, prepared figures and wrote the manuscript. SD-H analyzed the data, prepared figures and wrote the manuscript. EPH conducted experiments. TF conducted experiments. OFO designed experiments, supervised MHCN and EPH, oversaw analysis and interpretation of data, acquired funding and wrote the manuscript. YMN designed experiments, supervised MHCN and SD-H, oversaw analysis and interpretation of data, acquired funding and wrote the manuscript.

The manuscript has been read and approved by all authors. All 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. All authors state that all unprocessed data are available, and all figures provide accurate presentations of the original data.

Corresponding author: YMN takes full responsibility for the submission process and may be contacted about any aspect of the work.

Funding sources

MHCN was a recipient of an Irish Research Council Ph.D. Scholarship (GOIPG/2019/4514). This work was supported by Research Ireland (formally Science Foundation Ireland) under Grant Number 19/FFP/6820 and the Health Research Board Ireland [ILP-POR-2017-033].

Author disclosures

The study funders, Irish Research Council, Research Ireland and Health Research Board had no role in the data collection, analysis, interpretation, or writing of the report. YMN and OFO have received funding from Marigot Limited. YMN has received honoraria from Yakult as an invited speaker and OFO has received funding for unrelated contract research from Alkermes plc. and an honorarium as an invited speaker at a meeting organized by Janssen. All other contributors have confirmed that no conflict of interest exists.

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