Genomic Press

Psychedelics

The Journal of Psychedelic and Psychoactive Drug Research

Volume 1 | Number 3 | May 2025

Psychedelics

Unveiling the Mind's Therapeutic Frontier

Your research deserves visibility within the scientific community. We connect groundbreaking psychedelic studies with clinicians, researchers, and policymakers through thoughtful scientific communications and peer engagement. Each publication contributes to advancing this vital therapeutic frontier.

genomicpress.com

pp.genomicpress.com

Genomic Press
Psychedelics
The Journal of Psychedelic and Psychoactive Drug Research

pp.genomicpress.com

Genomic Press
Psychedelics
The Journal of Psychedelic and Psychoactive Drug Research

Psychedelics is published by Genomic Press.

SCOPE: *Psychedelics: The Journal of Psychedelic and Psychoactive Drug Research* aims to publish side by side premier papers in psychedelics along with outstanding contributions in other psychoactive substances. Our scope encompasses all compounds that affect consciousness and cognition. This ranges from classical psychedelics to the full spectrum of psychoactive substances including stimulants (cocaine), cannabinoids (marijuana), entactogens (MDMA), dissociatives (ketamine), plant-derived substances (kavain), and novel compounds including drug discovery approaches. This multidisciplinary journal spans molecular mechanisms to therapeutic applications, neuroscientific discoveries to sociocultural analyses. We invite submissions across methodologies from fundamental pharmacology and clinical studies to psychological investigations and societal-historical perspectives advancing our understanding of how these substances interact with human biology, psychology, and society.

MANUSCRIPT SUBMISSION: Authors are required to submit their manuscript electronically through our submission portal at url.genomicpress.com/2r53yz73. Detailed Author Instructions are available at url.genomicpress.com/zasktekn.

PUBLISHER: All business correspondence, inquiries about sponsorship opportunities, inquiries about advertising, and all customer service inquiries, including those related to Open Access and Article Processing Charges should be addressed to Genomic Press, 580 Fifth Avenue, Suite 820 New York, NY 10036, USA, +1-212-465-2548, support@genomicpress.com. Publishing Manager: Ma-Li Wong.

SOCIAL NETWORKS: Reach us through X or Instagram (both: @genomicpress) or LinkedIn (company/genomic-press).

DIGITAL ACCESS POINT: *Psychedelics* is available online at url.genomicpress.com/2s4ebkb9. For the actual version of record please always check the online version of the publication. Visit the journal's home page for details on aims, scope, mission, values, Editor-in-Chief, Editorial Board, author instructions, to learn more about our views on scientific integrity and peer review, and for updates.

ARTICLE PROCESSING CHARGES (APC): Writers contributing to *Psychedelics* are required to pay an article processing fee (APC), which is set upon the manuscript's acceptance. This charge is waived until 30 April 2025. From 1 May 2025 to 31 December 2025, we will have a promotional global APC rate of €1000/500 for submissions from within the European Union, £860/430 for those from the United Kingdom, CHF 1000/500 for those from Switzerland, JP¥170,000/85,000 for Japanese entries, and USD$990/495 for the United States and all other international submissions, with applicable local taxes. Specific APR rates are listed in the Author Instructions. We offer two APC rates: the higher rate is for regular-length papers and the lower rate is for shorter/brief submissions.The APC rates will be re-assessed in 2026. Papers originating primarily from countries classified as by the World Bank as low income will have a full APC waiver; those from lower middle-income countries that also have an annual gross domestic product (GDP) of less than 200 billion US dollars will have a 50% APC discount. We will entertain other requests for APC waivers or discounts on an individual basis. It is essential to apply for any such concessions at the time of manuscript submission, as we cannot entertain such requests during the manuscript review process or after manuscript acceptance.

SUPPLEMENTS: Until 31 December 2026, we will not have any supplements: all articles will be published in our regular issues.

REPRINTS AND PERMISSIONS: For information on reprint and permission requests, including instructions for obtaining these online, please e-mail us directly at: support@genomicpress.com.

ARTWORK: Journal imagery includes: (1) materials provided by authors or created by professional designers (commissioned or contributed), (2) stock photos from licensed commercial sources or copyright-free repositories, and (3) visuals created through very extensive human-AI collaboration (using DALL-E, Claude by Anthropic, or Grok created by xAI). All journal-created images are licensed under CC BY-NC-ND 4.0 and may be reproduced with proper attribution for non-commercial, unmodified use.

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

Psychedelics

Table of Contents

Volume 1 • Number 3 • May 2025

Cover Art

Cover Image: A laboratory mouse reaches toward an illuminated lightbulb in a vibrant, psychedelic-inspired setting, symbolizing the enhancement of cognitive flexibility following psychedelic treatment. The architectural columns frame a scene where traditional neuroscience meets the transformative potential of psychedelic research, while rainbow-hued patterns evoke the neural plasticity changes induced by serotonin 2A receptor activation. This artistic representation captures the key finding by Brouns et al. that a single dose of the psychedelic 25CN-NBOH produces sustained improvements in reversal learning and cognitive adaptability lasting weeks after administration, as demonstrated through automated behavioral paradigms (pages [29–35]). The imagery reflects the emerging understanding of how psychedelics may restore cognitive flexibility impaired in depression, PTSD, and neurodegenerative conditions through promotion of structural remodeling in the prefrontal cortex.

Provided by Omar J. Ahmed, CC BY 4.0

This issue is now available at https://url.genomicpress.com/6rarafbd.

Genomic Press

Amplifying discoveries across global networks

4,000 news stories ▪ 35 languages ▪ 4M+ social media views
We highlight the articles you publish with us to the entire research community through social media and the scientific press, with thoughtful press releases that showcase your work.

genomicpress.com

pp.genomicpress.com

Psychedelics

OPEN

EDITORIAL

Psychedelics, Yes—but Not Only: Redefining the boundaries of consciousness research as part of humanity's ongoing attempt to transcend our incompleteness

Psychedelics May 2025;1(3):1–2; doi: https://doi.org/10.61373/pp025d.0014

Launching a new journal is rarely the beginning people imagine it to be. It is not the first word, but the latest entry in a conversation already unfolding; in fits, in fragments, and in contradictions. *Psychedelics* enters the scholarly domain not with a thesis, but with a question: How should we think, write, and research consciousness in a landscape where definitions erode faster than they are drawn?

From the outset, our journal's indexed title, *Psychedelics*, has served a practical purpose. It signaled the core of our focus: compounds that alter perception, interrogate the self, and hint at pharmacological poetry once dismissed as hallucination. But even in our earliest planning, we knew this name alone could never hold the full scale of what we hoped to publish.

So we edited our subtitle. Not for flair, but because the original left something unsaid. It is now:

The Journal of Psychedelic and Psychoactive Drug Research

This is not rebranding. It is a quiet correction of what was always slightly misaligned. In truth, we were never just about psychedelics. We were always about the pharmacopeia of mind alteration: about those molecules, interventions, and subjective thresholds that force psychiatry, neuroscience, and the humanities to speak to one another, often uncomfortably.

There is, of course, precedent for this kind of reframing. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) has passed through successive editions in search of definitional coherence. Yet with each attempt, as I have written elsewhere, it manages only to get ready an unfinished and unconvincing edition (1). Borrowed from Drummond de Andrade that metaphor states: "The problem is not to concoct [ourselves]. [The problem] is to be concocted hour after hour without ever attaining our own convincing edition[1]" (2) (see Fig. 1). It is not only about the DSM. It is about science. About our journals. It is about us. We are forever concocting a version of ourselves that will never be a satisfying and finished product. At a deeper level, are psychedelics the latest tools in our endless search for the unattainable best version of ourselves?

And so, this editorial is not an announcement but an acknowledgment. A statement of publishing continuity masquerading as change. *Psychedelics*? Yes. But not only. Not only serotonergic. Not only hallucinogenic. Not only the easily narrativized compounds that lend themselves to funding cycles and headlines.

We are interested in MDMA. In ketamine. In ibogaine. Not because they fit a model, but because they do not. They exist at the margins as compounds that resist categorization, pharmacologically unruly, never quite settled within any taxonomy. What exactly makes something "psychedelic"? Is it its receptor target? Its cultural trajectory? The kind of story it provokes in the clinical encounter? Each of these is partly right, and wholly insufficient. The boundaries we rely on are "concocted hour after hour without ever attaining our own convincing edition." Those boundaries may be useful, but they are never final. Ultimately, our compounds of interest are part of humanity's ongoing attempt to transcend our incompleteness. We invite our readers to consider not just the classifications of these substances, but their deeper meaning in human experience.

Figure 1. The unfinished process of creation. The image illustrates the endless process of revision and reformulation described by Drummond de Andrade, where humans continually attempt to compose definitive versions of knowledge and self without ever reaching completion. From "Diagnosing Madness," by Julio Licinio, 2013, *Science*, 340(6139), p. 1406. Illustration by Joe Sutliff/www.cdad.com/joe. Reprinted with permission from AAAS.

So we reframed a subtitle. Not to embellish, but because the original title left something unsaid.

Let me then say this clearly, if not plainly. Our expectations remain exactly where they have always been. The work we publish must show its thinking. It must stand up, not through flourish, but through reason, through structure, and through data that does not fall apart when looked at closely.

But this is also true: ideas do not always resolve on schedule. Some arrive half-shaped. Others take the long way around, circling the issue until something more honest begins to take form.

We have room for writing that resists the urge to wrap things up. Sometimes, staying with the discomfort tells us more than reaching a

[1] "O problema não é inventar. É ser inventado hora após hora e nunca ficar pronta nossa edição convincente."

Received: 21 April 2025. Accepted: 25 April 2025.
Published online: 6 May 2025.

quick conclusion. It may take longer. It may feel unfinished. That, in itself, can be a form of clarity as we accept the unattainability of "our own convincing edition" – the permanently elusive ideal version of ourselves.

We know what it is to work inside incomplete systems: clinical, diagnostic, and epistemic. And we know that even in their perennial incompletion, these systems shape lives. That is why we publish. Not to finalize, but to keep going. To revise the conversation, rather than to end it.

So to our readers, authors, and critics: anticipate contradiction. Some compounds will not fit. Some theories are still in the middle of becoming something else. Because the mind, like the molecules we study, was never meant to be confined to the box it arrived in.

Julio Licinio[1]
[1]*Editor-in-Chief,* Psychedelics*, Genomic Press, New York, NY 10036, USA*
✉ *e-mail: julio.licinio@genomicpress.com*

References

1. Licinio J. Diagnosing madness. Science. 2013;340(6139):1406–1407 DOI: 10.1126/science.1236286.
2. Andrade, Carlos Drummond de. *Corpo*. Companhia das Letras, 2005, 120 pp. ISBN: 9788543803180.

pp.genomicpress.com

Psychedelics

OPEN

INNOVATORS & IDEAS: RISING STAR

Michael A. Wheeler: Psychedelics and neuroimmune circuits—what a strange trip, indeed

Psychedelics May 2025;1(3):3–6; doi: https://doi.org/10.61373/pp025k.0011

Keywords: Neuroimmunology, psychiatry, psychedelics, genomics, glia, inflammation

In a thought-provoking Genomic Press interview, Dr. Michael Wheeler emerges as a brilliant scientific innovator at the intersection of neuroscience and immunology. As an Assistant Professor at Harvard Medical School and an investigator at Brigham and Women's Hospital, Wheeler's groundbreaking research explores how brain-immune communication shapes our behaviors and emotions. His innovative laboratory weaves together genomic screening, single-cell technologies, and behavioral studies to unravel the fascinating dialogue between peripheral immune cells and brain function. Most remarkably, Wheeler's NIH-funded research has shown that psychedelics like psilocybin can reverse stress-induced fear behaviors by targeting a previously hidden neuroimmune pathway connecting inflammatory cells in the meninges to critical brain regions controlling emotions and rewards. This groundbreaking work has just been further validated in a *Nature* article (23 April 2025, DOI: 10.1038/s41586-025-08880-9) showing how psychedelics regulate the complex interplay between brain and immune cells in fear responses. By revealing how psychedelics modulate not just neurons but also immune responses, Wheeler's paradigm-shifting research opens exciting new therapeutic possibilities for depression, addiction, and stress-related disorders. Through his warm, authentic scientific approach and deep curiosity about mind-body connections, Wheeler represents a new generation of researchers redrawing the boundaries between psychiatry and immunology to transform our understanding of mental health.

Part 1: Michael Wheeler – 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 community growing up did not have a lot of resources, so I was not exposed to bench research until I went to college. But I had incredible teachers and mentors as a kid that exposed me to important ideas. In particular, I think the moment that inched me closer toward a career in science rather than the humanities (which I loved) was during my Psychology class in high school thinking about consciousness; both its essence and subjectivity and thinking about the lack of control we have over our conscious experiences. That early fascination with the involuntary nature of thought eventually shaped my interest in how external forces—like stress or trauma—can reshape our inner world. I also loved math. Therefore in college, I pursued both the humanities and science/engineering, and really had trouble selecting a path. I did internships in preparation for law school, medical school, and graduate school. My first exposure to basic science was as a college freshman. I was privileged to join the lab of Hongjun Song at Johns Hopkins, training under Michael Bonaguidi, who now runs his own lab at USC. Besides the techniques, I took 2 major lessons from my time as an undergraduate in that lab. The first is that you cannot do great science alone, everyone needs a great team. The second is how to strategize building a scientific story from the ground up, which is probably the aspect of science that most captivated me.

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

Counterintuitively, when I decided to pursue a PhD in Neuroscience was during my internship at the Public Defender's office in the Baltimore City Capital Defense Division. I felt that the actions of the people we defended were so inextricably linked with their environmental circumstances, inclusive of physical or emotional abuse beyond their control, that I was desperate to understand the inner workings of their minds. Since that experience, my long-term goal has always been to get at the environment-brain interplay to try and, naively, remediate some of the socially inflicted human suffering that I witnessed there. However, I am more optimistic that we can begin treading that path as I have learned more about neuroimmune mechanisms in a laboratory setting.

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 have been super fortunate to work in a Department that values developing and retaining former trainees and facilitating their independence. Choosing mentors who care about me as a person and a scientist has been the most career-defining factor. Whether it is the Song lab taking in an undergraduate with zero knowledge of science, my graduate school mentors Chris Deppmann and Ali Güler, who fostered my growth, or my postdoctoral mentor Francisco Quintana helping me during my transition to independence, or even my excellent bosses now like Vijay Kuchroo, Howard Weiner, and Tracy Batchelor, I feel fortunate to have had these mentorship experiences.

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?

One of the most intimidating choices I made was joining the lab of an Immunologist during my post-doc. I only trained in Neuroscience at that point, so when I looked at Francisco's papers on dendritic cells and T cells, I was nervous about what I was getting into. However, I lucked out by having extraordinary lab mates from different fields. Francisco allowed us to connect and work together, allowing us to do some exciting things. This experience ultimately allowed me to learn a new scientific language. Moreover, now, I am a faculty member of the Gene Lay Institute of Immunology and Inflammation, contributing to Neuroimmunology while continuing to learn from some of the most respected figures in immunology.

Received: 16 April 2025. Revised: 23 April 2025. Accepted: 24 April 2025.
Published online: 6 May 2025.

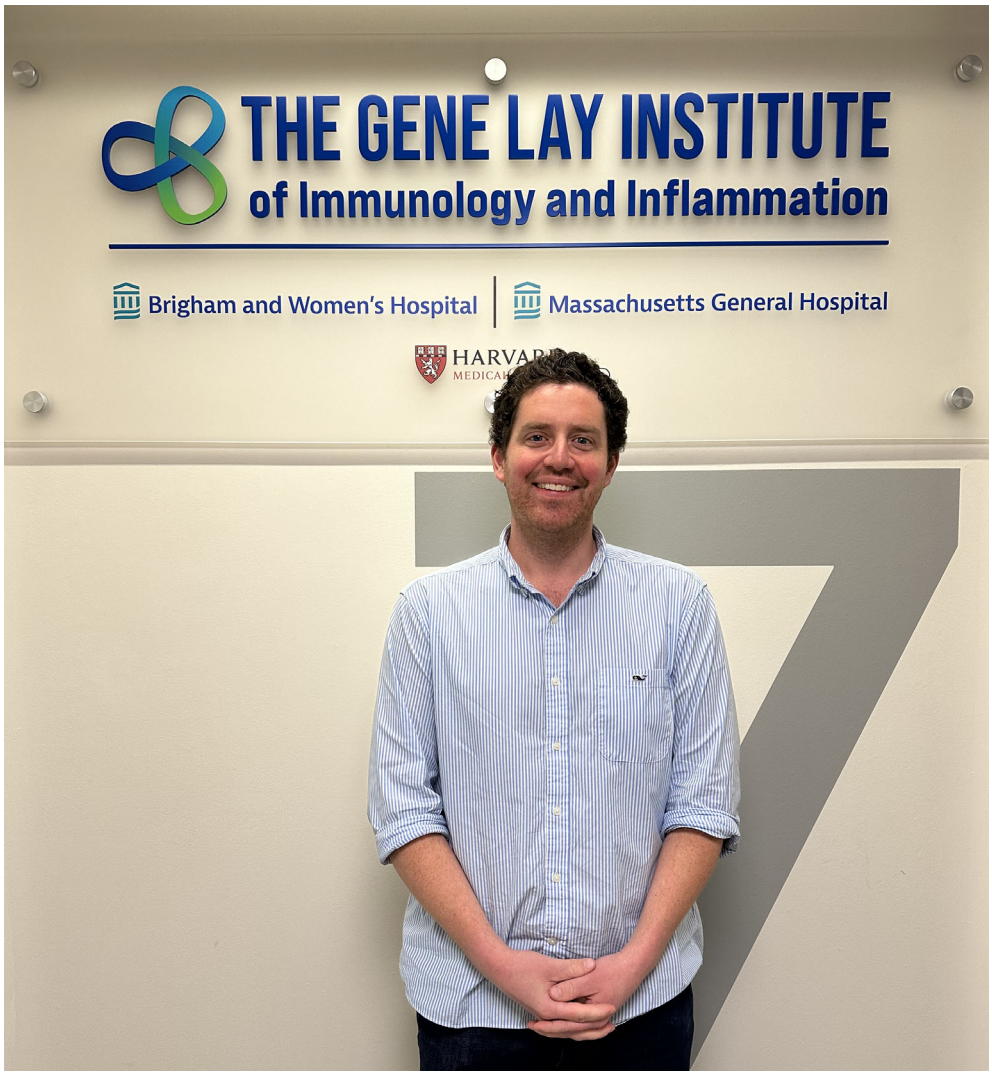


Figure 1. Michael A. Wheeler, PhD, Harvard Medical School, Brigham & Women's Hospital, USA.

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

Most important is to read, read, and read the literature to stay current with the latest work, as you are never the first to find something. Related to this, I also love incorporating new methods and analytical frameworks to study problems I am interested in. It is crucial to use orthogonal (and novel) methods to validate conclusions, perform time courses, and analyze independent variables through screening platforms. These types of designs are what we like to do in my lab. On a personal level, it is important to make every team member realize how much they offer and to emphasize everyone's unique skill sets. I have drawn this principle from every lab I have trained in.

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

We are deeply interested in establishing links between the brain and immune system to uncover whole-body therapeutic targets in psychiatry and inflammatory diseases. Just this week, we have published new findings in *Nature* on 23 April 2025 (DOI: 10.1038/s41586-025-08880-9) that really tie into this goal. We found that astrocytes in the amygdala use a specific receptor called EGFR to limit stress-induced fear. When chronic stress disrupts this signaling, it leads to a cascade involving brain-resident cells and immune cells that ultimately increases fear behavior. What is fascinating is that psychedelic compounds can reverse this entire process: they reduce the immune cell accumulation in the brain meninges coincident with reducing fear behaviors. It is part of our broader effort to map these brain-body communication circuits, almost like creating that wiring diagram I mentioned earlier. I am particularly excited about the clinical validation aspects of this work. Altogether, this work suggests that the immune system also controls psychedelic-induced brain plasticity. It suggests psychedelics could be therapeutic not just for neuropsychiatric conditions, but potentially for other inflammatory diseases as well.

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

I am excited about the prospect of identifying brain-body communication loops as a fundamental feature of physiology. Often, we think of mental health disorders based on their behavioral symptoms. However, we are likely leaving much underlying biology on the table by focusing solely on the brain. I am hopeful that we can bring structure to the field of Neuroimmunology and define the topology of neuroimmune interactions—almost like charting a wiring diagram for how mind and body stay in dialogue, which we can do through many of the sensitive single-cell approaches now available, some of which we helped develop. I hope that this leads to a revolution in thinking about therapeutic agents to treat neuropsychiatric disorders.

Figure 2. Members of the Wheeler lab are out having dinner in Boston in early 2024.

What do you most enjoy in your capacity as an academic or research rising star?
As a PI, my favorite part is bringing people into the lab and onto our team with completely different scientific (and personal) backgrounds to have everyone work together. This facilitates cross-pollination between ideas that could only happen on the organizational level. Importantly, everyone makes significant contributions, grows as a scientist, and drives us in new directions. There is way too much for me to learn or know individually, so relying on such a skilled and motivated team is exciting.

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?
Now, as ever, one of the most important things we scientists must do is engage with non-scientists about our work and explain how scientific consensus is distinct from something akin to belief. We need effective communicators to relay complex scientific findings authentically and groundedly: What was done? What are its limitations? What is next? What are the real-world implications? When "science" the discipline is presented as a monolithic, dogmatic enterprise, it may evoke suspicion. And that is understandable—scientists thrive on skepticism, and we should expect the same from the public.

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 learned to love movies from my mom and have been a regular at the Coolidge Corner Theater in Brookline for years. I even have a personalized seat there. I love watching movies that introduce avant-garde ideas or new filmmaking styles.

Part 2: Michael Wheeler – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
Openness to change.

Among your talents, which one(s) give(s) you a competitive edge?
Resilience in the face of failure.

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

What is your current state of mind?
Excited for the future.

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

What is your idea of perfect happiness?
I learned about a Japanese practice called "forest bathing," which involves spending time in nature. I love "city bathing," which involves taking long walks in Boston (and other cities), particularly in busy areas, to feel how alive everything is.

When and where were you happiest? And why were you so happy then?
When my wife and I first visited Paris in the springtime, we wandered through the streets, found a fantastic restaurant called La Mascotte, and ate outside amidst the bustle. It was Hemingway's "moveable feast," Godard's *Breathless*, just dynamic bliss.

What is your greatest fear?
Not savoring the present.

What is your greatest regret?
I try not to regret anything—mistakes tend to be good teachers.

What are you most proud of?
My two kids it is the first thing I have done that will outlive me.

What do you consider your greatest achievement?
I am hopeful I have not done it yet, though building a thriving, collaborative lab is something I am deeply proud of.

What or who is your greatest passion?
My family.

What is your favorite occupation (or activity)?
I love going out to nice restaurants.

What is your greatest extravagance?
It would not hurt if the restaurant adjoined a nice hotel.

What is your most treasured possession?
An autographed UFO drawing from Bob Lazar.

Where would you most like to live?
Paris.

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

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

What do you consider the most overrated virtue?
The solitary genius.

What do you most value in your friends?
Authenticity.

Which living person do you most admire?
Werner Herzog – his work is bold, creative, and feels deeply human.

Who are your heroes in real life?
Santiago Ramón y Cajal. He was such a meticulous scientist and dominant thinker whose observations are still alive today.

If you could have dinner with any historical figure, who would it be and why?
Socrates—a deadly combination of brilliant and fun.

Who are your favorite writers?
I am enthralled by Robert Caro's biographies of Lyndon Johnson and am waiting impatiently for the fifth and final volume. I also just read *The Sellout* by Paul Beatty, which is so densely brilliant that its only comparison is *Infinite Jest*. Two other books I recently read that I found profound and unique were *Barracoon* by Zora Neale Hurston and *The Twilight World* by Werner Herzog, both about how environments profoundly shape identity.

Who are your heroes of fiction?
I have always been a Sherlock Holmes fan, and for that matter, Dr. House.

What aphorism or motto best encapsulates your life philosophy?
A jug fills drop by drop.

Boston, Massachusetts, USA
10 April 2025

Michael A. Wheeler[1]
[1] *The Gene Lay Institute of Immunology and Inflammation, Ann Romney Center for Neurologic Diseases, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, USA*
✉ *e-mail: mwheeler0@bwh.harvard.edu*

pp.genomicpress.com

Psychedelics

OPEN

INNOVATORS & IDEAS: RISING STAR

Katarina Leão: Links between the auditory and limbic systems, with a focus on the effects of unconventional novel treatment options, such as psychedelics and cannabis extract

Psychedelics May 2025;1(3):7–9; doi: https://doi.org/10.61373/pp024k.0001

Keywords: Noise-induced tinnitus, tinnitus-related anxiety, psychedelics, research training, women in science

Katarina E. Leão, PhD, is an associate professor at the Brain Institute at the Federal University of Rio Grande do Norte, Natal, Brazil. She is vice-coordinator of the postgraduate program in neuroscience (2013–2017 and 2023 – current) and spent 2020 as a visiting professor at the Karolinska Institute/Uppsala University, Sweden. She is head of the Hearing and Neuronal activity lab researching neuronal mechanisms of noise-induced tinnitus and tinnitus-related anxiety. Dr. Leão recently joined the ongoing interview series by Genomic Press, discussing her professional endeavors and personal experiences.

The Genomic Press Interview Part 1: Katarina Leão – Life and career

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

I grew up in a small steel factory town in Sweden, in a non-academic family. I worked as a nanny in South Carolina, USA, straight after high school to improve my English. In 1999 I started studying Pharmaceutical Bioscience at Gothenburg University, Sweden, convinced I wanted to work in the pharmaceutical industry. Having developed preclinical studies for my master project, I had an opportunity to do my final project abroad and by stitching together several travels grants I managed to make it to Australia. Here I aimed to visit my aunt and cousins living in Canberra, and thereby applied to the John Curtin School of Medical Research (JCSMR), at the Australian National University (ANU). The two main research lines at that institute were immunology and neuroscience, and knowing both were competitive, I opted for neuroscience. This was a strike of sheer luck as I ended up in a world renown neuroscience department, with particularly strength in whole-cell patch clamp electrophysiology being applied by almost every lab there. In this dynamic and very social research environment, I fell in love with neuroscience and specifically ion channels and action potentials. Here is also were I became friends with a group of Brazilians.

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

I carried out my PhD in the lab of Professor Bruce Walmsley at JCSMR, ANU, Australia, studying membrane properties of brainstem neurons from deaf and sound stimulated mice. Returning to Sweden in 2007, I gave up on the pharmaceutical industry plan, but had bureaucratic issues for getting a postdoc stipend as a Swede. Finally, I ended up at Uppsala University, in a lab producing different transgenic mice lines for studying spinal cord circuits. This was a humbling experience as I knew close to nothing about genetic engineering and spinal cord physiology. However, the lab of Dr Klas Kullander was well funded and I convinced the PI that they needed to add electrophysiology as a core technique and was then entrusted to order equipment and assembled their first patch clamp rig. The lab developed more transgenic lines than they had time to test but one caught my attention, the Chrna2-cre mouse (now considered one of the most specific cre-lines in neuroscience). This led to collaborative work together with my then Brazilian husband, studying a particular hippocampal interneuron, and a publication in *Nature Neuroscience*. After years as a postdoc, I heard about the international neuroscience institute recently established in Natal, Brazil, and the chance of getting tenured positions. With some hard work this became reality in 2013. To have job stability as the industry usually provide, and being able to do basic research on my terms without paying for lab space, is a dream come true, actually more than I had dared to hope as a young female PhD student. Now I am proud to be one of four female PIs at the Brain institute, UFRN, Natal, and I enjoy living in a tropical, sunny climate.

Figure 1. Katarina Leão, PhD, Universidade Federal do Rio Grande do Norte, Brazil.

Received: 11 January 2024. Accepted: 12 January 2024.
Published online: 25 January 2024.

Please share with us what initially piqued your interest in your favorite area of research or professional focus.
My fundamental research interest is neuronal excitability and how it is dynamically shaped by distinct voltage-gated ion channels regulated by genes and sensory experiences. Specifically, my last project as a PhD student has shaped my research interest, seeing how sound presented for just one hour, dramatically changed gradients of ion channels in circuits of sound localization. This showed me how plastic the brain is, where just increased activity for one hour triggered distinct c-Fos activity and reorganization of certain voltage-gated ion channels. As PI I returned to the auditory field, focusing on the challenging question of mechanisms behind perception of noise-induced tinnitus. Here, I carry with me my postdoc experiences of working with transgenic animals and hippocampal electrophysiology both in vitro and in vivo.

What kind of impact do you hope to achieve in your field through your focus on your specific research topics?
Specifically, I hope to contribute towards treatments of tinnitus and tinnitus-related anxiety. I study tinnitus without concurrent hearing loss, often occurring in younger individuals and causing a life-long negative impact on their quality of life due to increased stress and anxiety. I strive to increase the level of detail in this field by identifying variations in subtypes of neurons, specific ion channel perturbations, and alterations of genes in specific areas. As I have worked in several anatomical areas, with different cell types, I can often draw useful parallels from other fields, leading to new ways of thinking.

Could you tell us more about your current scholarly focal points within your chosen field of science?
My research focus is on the mechanisms of perception of noise-induced tinnitus in a mouse model. Here we implement genetic tools and investigating links between the auditory and limbic systems by studying the impact of loud noise on cortical neurons and also on hippocampal circuits. As noise-induced tinnitus is highly correlated to anxiety and stress, this is also something we investigate looking at genetics, electrophysiology and behavior, and also examining the effects of unconventional novel treatment options, such as psychedelics and cannabis extract.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences, that you uphold within your own research environment?
We have weekly journal clubs, taking turn presenting current topics, often using the journal club to collectively tackle methodologically complex papers. I speak mostly English in the lab to teach students the global scientific language. We collaborate and help each other, and celebrate publications with cake and sparkling wine, all according to my PhD experience.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that you think warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?
This is a topic I have interest in and have given talks about. For example, I believe women need to be mentored into leading positions in science, and locally women need to support other women in science in a more outspoken manner. The recognition of maternity leave in the CV is a small but crucial step towards accounting for lost years in science when applying for competing positions with men. Cultural diversity in science needs to be urgently increased, at grass root levels, with direct incentives. Removing or decreasing publishing fees for a larger group of developing countries is also fundamental for equal opportunities.

What do you most enjoy in your capacity as someone deeply engaged in academic and research activities?
I enjoy seeing the transformation of students into researchers, see them overcoming struggles, and gaining academic success. I am particularly happy when I can help students towards international travel grants where they can partake in neuroscience courses and conferences, networking by making new friends, and at the same time see the world. I had the luck of travelling considerably during my academic trajectory and now I try to pay it forward. More so, I enjoy it when projects reach the point of becoming manuscripts with complex figures. It gives me closure and a sense of organization in the otherwise often complex and surprising world of basic research.

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 kids and friends, having everyone's kids around playing in the pool, while enjoying heartful conversations. I also love to travel to/with my boyfriend and going out to small street-side bars and listen to music.

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

What is your idea of perfect happiness?
Having a loving family and lots of friends, living in a comfortable home, having a secure and interesting job in science and living in a democracy that cares for its citizens and the environment.

What is your greatest fear?
Brazilian bureaucracy! No, that was a joke. I actually respect it, and it has taught me patience and provided me with a greater understanding of this large country that I live in and love.

Which living person do you most admire?
My parents. My dad is a rare mix of water purity expert, dyslexic, diving instructor, sonar inventor, car mechanic, yoga instructor, hunter and carpenter. I kind of grew up with MacGyver as my dad, and a mum with green thumbs making the house and garden full of exotic plants, and always with time to bake breads and cakes, despite having 3 kids, as my dad was kept busy by his activities.

What is your greatest extravagance?
I am a bit fearless and constantly push my comfort zone, not always voluntarily so, but usually things work out in the end. I think growing up in a safe and stable home in a small town gave me core resilience, and traveling while young made me brave.

What are you most proud of?
My kids.

What is your greatest regret?
I have few regrets as I believe all experiences teach us something useful. Perhaps I regret not going to the electrophysiology course at Stradbroke Island, Australia, as a PhD student. I think it would have liked it a lot, but then I thought it was too late to go as a second year PhD student. Little did I know then that science is a constant learning.

[1] In the late nineteenth century various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is the quality you most admire in people?
Kindness and open-mindedness.

What do you consider the most overrated virtue?
If you had high grades in school as a kid. Paradoxically, it is often those who achieve moderate grades, rather than stellar ones, who reach the zenith of their professional journeys.

What is your favorite occupation?
Scientist and teacher.

Where would you most like to live?
By the ocean in a not too big city.

What is your most treasured possession?
Not sure I have one, but perhaps speakers and headphones of good quality. I love music and I need good quality sound.

When and where were you happiest? And why were so happy then?
I guess I am happy now. Life is a journey full of adventures, but to feel loved and secure, with a permanent university position, makes me very happy.

What is your most marked characteristic?
Organized.

Among your talents, which one do you think gives you a competitive edge?
I would say the combination of a mixed scientific background, enjoying reading papers, having good collaborations and that I am organized.

What is a personality/characteristic trait you wish you had?
Charisma as a public speaker.

What do you consider your greatest achievement?
Publishing our research with cutting edge techniques in high impact journals while planning and waiting for our current institute being built. In the first 8 years (that was supposed to be 4 years) we were in a suboptimal rented institute with limited research space; we even had to use bathroom space to fit equipment. Luckily, the spirit of all researchers was high and students worked hard, doing shifts to use equipment and sharing desk space. I am very proud of being part of the Brain institute of today and to be based in the building that we designed according to the highest of international standards.

What do you most value in your friends?
Sincere conversations and our wine-night gatherings.

Who are your favorite writers?
Salman Rushdie, William Gibson, Douglas Adams, Becky Chambers to mention a few.

Who are your heroes of fiction?
Lisbeth Salander in the Millennium trilogy books is a great fictional hero.

Who are your heroes in real life?
Dr Kerstin Schmidt, leading our institute, Greta Thunberg for being so prominent in the worldwide movement on ways of decreasing global warming.

What aphorism or motto best encapsulates your life philosophy?
"Show me, don't tell me." This applies to me as a supervisor as well as to my students.

Katarina Leão[1]
[1]*Federal University of Rio Grande do Norte (UFRN), 59078-970 Natal, Rio Grande do Norte, Brazil*
✉ *e-mail: katarina.leao@neuro.ufrn.br*

pp.genomicpress.com

Psychedelics

OPEN

INNOVATORS & IDEAS: RESEARCH LEADER

Stephen Ross: Psychedelic-assisted therapies for difficult-to-treat psychiatric and medical disorders

Psychedelics May 2025;1(3):10–13; doi: https://doi.org/10.61373/pp025k.0017

Keywords: Psychedelics, psilocybin, psychotherapy, novel therapeutics, psychiatry

Professor Stephen Ross is a prominent faculty member in the Departments of Psychiatry and Child and Adolescent Psychiatry at the New York University (NYU) Grossman School of Medicine who has transformed the landscape of psychedelic research since 2006. In this Genomic Press Interview, Dr. Ross reveals how as co-director of the NYU Langone Center for Psychedelic Medicine and director of its research training program, he has spearheaded groundbreaking clinical trials demonstrating the remarkable efficacy of psilocybin-assisted psychotherapy for treating existential distress in advanced cancer patients, alcohol use disorder, and major depressive disorder. His 2016 landmark study showing rapid, substantial, and enduring improvements in cancer-related anxiety and depression following single-dose psilocybin treatment garnered global attention with 1.7 billion media views. It rejuvenated a dormant field of psychiatric research. Despite early career warnings that psychedelic research was "a road to nowhere," Dr. Ross persevered to secure the first National Cancer Institute grant for psychedelic research in over 50 years, establishing NYU as a pioneering institution in psychedelic medicine. Throughout his 25-year career at NYU, he has balanced research innovation with clinical leadership, directing Bellevue Hospital's substance abuse division for 12 years, receiving numerous teaching awards, and maintaining a compassion-driven approach inspired by early experiences with hospice care. His current research extends beyond psychiatry into pain management, early-stage cancer interventions, and the potential anti-inflammatory properties of psychedelics, reflecting his commitment to developing novel therapeutics for conditions with substantial unmet needs and public health burden.

Part 1: Stephen Ross – Life and Career

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

I was born in South Africa and moved to Los Angeles with my family when I was 7. Inspired by my parents and a black African woman who took care of me in South Africa, as far back as I can remember, I wanted to pursue a career in medicine to help others. On a track to be a cardiothoracic surgeon, the experiences of family members of mine motivated me to pursue a clinical and research career in psychiatry and addiction medicine. As a teenager, I spent several summers accompanying my mom, a hospice volunteer worker. This had a profound impact on me and taught me the importance of helping people die with psychological, emotional, and spiritual well-being. This experience inspired me later in my career to pursue clinical research in end-of-life care.

I went into medicine to help people. Early in my career, that would entail helping one person at a time in my psychiatric practice. Inspired by mentors at Bellevue Hospital, my focus evolved. I developed a desire to pursue clinical leadership that allowed me to help groups of people at a time. This culminated in me directing the substance abuse division at Bellevue Hospital for 12 years, overseeing a range of inpatient and outpatient programs that cared for thousands of patients annually. This experience galvanized my passion to pursue clinical research as a tool to help people on a larger scale by developing novel therapeutics to treat neuropsychiatric disorders where there is a substantial unmet need and public health burden.

Figure 1. Stephen Ross, MD, New York University School of Medicine, USA.

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

My interest in psychedelic clinical research began serendipitously one day in 2006 when my supervisor at the time, Dr Jeffrey Guss, walked into my office and asked me what I knew about the history of psychedelic research in psychiatry. I told him that I did not know what he was talking about and was unaware that psychedelics had ever been a significant part of psychiatry. Stimulated by our conversation, I was shocked to find out that, hidden in plain sight, psychedelics were extensively studied in psychiatry from the 1950s to the 1970s in the US and internationally with over 40,000 participants and over 1,000 articles published. Nowhere in my training, from medical school to general psychiatry residency to addiction fellowship training, did I ever hear about this exciting and significant part of psychiatric history. My interest was further piqued when I found out that the most promising therapeutic targets of psychedelic-assisted therapies (mostly with LSD) were alcohol use disorder as well as depression, anxiety, and existential distress in advanced cancer–since these were areas of interest to me. I came to understand that the promise of psychedelic therapy ended when the drugs escaped from the lab in the 1960s, were used extensively by the general public in unsafe settings, leading to serious adverse outcomes, and ultimately leading to this class of drugs becoming

Received: 30 April 2025. Accepted: 9 May 2025.
Published online: 10 June 2025.

illegal with the passage of the Controlled Substances Act of 1970. This prohibition effectively ended the promise of the first wave of psychedelic research so extensively that it was absent from all of my education and training. Soon after, Jeffrey Guss, MD, Anthony Bossis, PhD, and I formed the NYU Psychedelic Research Group in 2006 with the goal of starting a program of clinical research at NYU exploring the therapeutic potential of psychedelic-assisted psychotherapies. Our group was one of the first psychedelic research programs that helped spark the second wave of psychedelic research over the last 25 years.

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?

In 2021, along with my colleague Dr Michael Bogenschutz, we established the NYU Langone Center for Psychedelic Medicine, one of the first centers of psychedelic research to be established in the US, after receiving a $10M philanthropic gift. I am co-director of CPM and director of the center's research training program. The mission of CPM is to develop novel psychedelic therapies for some of the most difficult-to-treat conditions in psychiatry and medicine. Although psychedelic research to date has been concentrated within the field of psychiatry, the CPM seeks to expand this focus through the pursuit of promising clinical applications across health-related disciplines in medicine. As an example, we are actively researching psychedelics as a treatment for various pain and inflammatory conditions. Our pre-clinical branch investigates mechanisms by which psychedelics impact physical and mental health, and we have developed a training program for research scientists interested in careers in psychedelic medicine.

After forming the NYU Psychedelic Research Group in 2006 with several colleagues, we embarked on a pilot randomized controlled trial (RCT) assessing the safety and efficacy of single-dose psilocybin-assisted psychotherapy (PAP) to treat anxiety, depression, and existential distress associated with advanced cancer. We published our findings in 2016 and found that PAP produced rapid, substantial, and sustained (e.g., 6.5 months) improvements in anxiety and depressive symptoms associated with cancer. We also found that the intervention reduced existential distress and improved quality of life. Approximately 75% of the participants rated the psilocybin experience as one of their life's most spiritual, meaningful, and memorable experiences. This publication was considered a landmark in the field of psychiatry and psychedelic medicine. It was covered extensively internationally, was one of the biggest news stories in medicine in 2016–2017, garnering approximately 1.7 billion views, and was featured on the front page of the *New York Times* on 1 December 2016. It has been cited approximately 2000 times since its publication and is credited as one of the key events re-opening the field of psychedelic clinical research. I was shocked at the results of this trial, not expecting such rapid and robust clinical responses. This had a profound impact on me, especially since I learned almost nothing about palliative care during my medical training, and it reminded me of my positive experiences as a teenager witnessing people dying with peace and well-being in a hospice in Los Angeles. The findings from this trial emboldened me to pursue clinical research further using psychedelic therapies to help people with advanced cancer and other serious medical illnesses experiencing clinically significant psychiatric and existential distress. Attempting to replicate the findings of our pilot trial, along with colleagues, in 2022, we were awarded an RO1 from the National Cancer Institute to conduct the largest clinical trial of psychedelics to treat advanced cancer-related emotional and spiritual distress to date. This was the first grant ever given by NCI, one of the first awarded by NIH in over 50 years for psychedelic clinical research, and signaled an openness of NIH to reconsider funding this novel area of therapeutics. If in the future, psilocybin or other psychedelics were approved and prescribable medications in people with serious medical illnesses, such as advanced cancer, to be used in the context of psychotherapeutic platforms, it could be a significant development that opens up a pathway for clinical dissemination and public health impact internationally. Examples of care delivery settings would likely include cancer centers, palliative care programs, and hospices.

Towards the end of our pilot RCT of PAP in advanced cancer, as an addiction psychiatrist, I decided to tack in the direction of researching PAP to treat substance use disorders. This was the most promising area of clinical research during the first wave of psychedelic research, with data from 5 RCTs suggesting the efficacy of single-dose LSD-assisted therapy to treat alcohol use disorder (AUD). Teaming up with my colleague Dr Michael Bogenschutz, who was recruited to NYU in 2015, we conducted the first RCT assessing the efficacy of a two-dose psilocybin administration regimen, combined with psychotherapy, to treat AUD. Of all substance use disorders, AUD arguably represents the greatest public health threat in the US and globally when factoring in prevalence, preventable death, premature death, disability, healthcare/societal costs, adverse medical and neuropsychiatric complications, unintentional injuries, and its significant causal link to suicidal and violent behaviors. Current treatment approaches are limited in effectiveness. In 2022, we published our findings in JAMA Psychiatry that PAP produced rapid, robust, and sustained (e.g., 8 months) decreases in the percentage of heavy drinking days. This publication was covered internationally in the media and recognized as the pivotal psychedelic medicine breakthrough in 2022. Psychedelic therapies for substance use disorders are one of the most promising areas of clinical research with psychedelics. If larger trials continue to demonstrate safety and efficacy, it potentially opens up a pathway for clinical dissemination, including inpatient and outpatient SUD treatment programs.

Our pilot RCT of PAP in advanced cancer-related anxiety and depression was the first RCT to demonstrate that psilocybin produced rapidly acting and sustained (e.g., weeks to months) anti-depressant effects from single-dose administration. This led several biotech companies to invest in developing psilocybin therapy as a treatment for major depressive disorder (MDD), with two companies having received breakthrough status from the US FDA for this approach. I was a senior author on a phase 2, multi-center trial published in JAMA in 2023 that demonstrated that single-dose PAP in MDD is safe and produces rapid, clinically significant, and sustained (up to 6 weeks) reductions in depressive symptoms and functional disability. Several biotech companies are finishing up phase 3 trials of psilocybin therapy for MDD, with converging data suggesting safety and efficacy. This is the leading edge of psilocybin drug development and potentially opens up a pathway for psilocybin to become an FDA-approved and prescribable treatment for MDD within a few years. This could represent a paradigmatic shift and breakthrough in the therapeutics of MDD, arguably the most disabling brain-based illness in the world.

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?

My decision to pursue a research career in psychedelic medicine seemed like a big mistake in 2006 when I first started. Several of my research mentors told me that it was a terrible idea due to the intense societal and governmental stigma associated with the long shadow of the prohibition against psychedelics after the first wave of psychedelic research was shut down in the early 1970s. I was told that it was a road to nowhere, a career killer, and an area that would never again attract federal funding. Intrigued by the areas of psychedelic clinical research that appeared promising, such as addiction and end-of-life care, and perhaps being young and naïve in my career, I decided to keep putting one foot in front of the other and kept going. It was very challenging at first, but I slowly and meticulously worked through all of the roadblocks and barriers. Our first study with PAP in advanced cancer took a decade to complete, but the experience completely transformed my career and set me on a path to continue to focus on psychedelics as novel therapies for some of the most intractable conditions in psychiatry and medicine.

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

Habits: obsessive focus on achieving a goal; diligence; resilience- learning from and finding opportunities in the face of setbacks or failure; going deep into a topic.

Values: Finding meaning and purpose in helping others; working collaboratively with others and the power of group dynamics in fostering scientific creativity and innovation; the vital importance of ethical treatment of research participants.

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

Within my field of psychedelic psychiatry and medicine, I have several main areas of scholarly interest focusing on the treatment of difficult-to-treat disorders in psychiatry and medicine including: psychiatric and existential distress in advanced cancer and other serious medical illnesses; mood disorders such as MDD; substance use disorders, personality disorders, PTSD, and chronic pain. I am particularly active in the area of psychedelic therapeutics for cancer and other serious medical illnesses. I am more than halfway through my current NCI RO1 assessing the safety and efficacy of PAP to treat anxiety, depression, and existential distress in advanced cancer. Tacking from studying psychedelics in advanced cancer towards earlier staged cancers with substantial psychiatric morbidity, I am hoping shortly to begin a pilot RCT of PAP, funded by NCI, to treat clinically significant fear of recurrence in women with early-stage breast cancer. I am also the site PI of a biotech-funded multi-center clinical trial assessing the safety and efficacy of a short-acting novel psychedelic to treat adjustment disorder in cancer and other serious medical illnesses, which represents an extension of work I have done with PAP in cancer. I am also expanding my research focus on psychedelics to target chronic pain. I have developed a concept that I have submitted to NIH, picking up from work conducted in the 1960s, of an RCT of LSD-assisted therapy to treat metastatic cancer-induced bone pain. I am also focused on research with psychedelic therapies for MDD, being part of a phase 3 multi-center RCT (site PI) of psilocybin therapy for MDD, as well as a phase 2 multi-center RCT (site PI) of a short-acting novel psychedelic to treat post-partum MDD. I plan to continue my focus on psychedelic therapeutics for substance use disorders soon.

Apart from my clinical research with psychedelics as therapies for psychiatric and medical conditions, I was Principal Investigator (PI) of a study administering psilocybin to healthy volunteers, namely religious professionals. This RCT was conducted in conjunction with colleagues at Johns Hopkins. It was a follow-up to the famous Good Friday Experiment, conducted in 1962 by Walter Pahnke, that suggested that single-dose psilocybin administration to divinity students in a group setting, as compared to active placebo, produced mystical experiences and was associated with increased positive changes in attitudes and behavior at 6-month and 25-year follow-up. The study, published in May 2025 (DOI: 10.1089/psymed.2023.0044), found that in population of psychedelic-naïve clergy from various major world religions, psilocybin administration was safe and increased multiple domains of overall psychological well-being including positive changes in religious attitudes, including increased tolerance of other religions, and behavior as well as their vocation as a religious leader.

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

My goal is to continue to conduct rigorous clinical trial research with psychedelics to determine if they are safe and efficacious. My focus has been on research PAP as a novel treatment for three areas within psychiatry and medicine where there is a substantial unmet need and public health burden: major depressive disorder, existential distress in advanced cancer and other serious medical illnesses, and alcohol addiction. I approach these efforts with equipoise and neutrality, not knowing the outcome. Suppose the research continues to demonstrate safety and efficacy. In that case, I hope there is a process, in particular drug development with the FDA, that puts the interventions on track to be translated into clinical care to impact the lives of as many people as possible positively.

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

I love the opportunity to delve deeply into a topic with the ultimate goal of helping as many people as possible. I also greatly enjoy the opportunity to mentor junior scientists and see them grow and flourish in their research careers, with the ultimate goal of translating their passion for science into alleviating suffering.

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?

Within my field of psychedelic medicine, both historically and currently, the response of the press, general culture, and even the scientific community has tended towards hyperbolic responses, ranging from unbridled enthusiasm that psychedelics are a cure all for all ailments to beliefs that they are so harmful and dangerous that they need to be prohibited. I hope that through rigorous, unbiased, and meticulous scientific study, the truth about psychedelic therapies emerges so that we can develop a rationale and clear-eyed view of their therapeutic potential and risks.

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

In my leisure time, I love spending time with my wife and our two beautiful Boston Terriers. My favorite hobbies are travel, hiking, eating, and sailing.

Part 2: Stephen Ross – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?

Compassion towards others.

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

I am doggedly determined to achieve my objectives, never give up, and have always been able to be resilient, find opportunities, and grow in the face of adversity and failure.

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

I would like to be less anxious and fearful.

What is your current state of mind?

I feel a sense of stability and happiness that I have not experienced since childhood. I credit this to my amazing wife and our beautiful dogs, as well as being blessed by having two loving parents, a wonderful brother, and an extended network of supportive family members, friends, and work colleagues.

What is your idea of perfect happiness?

Snuggling in bed with my wife and our two dogs.

[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. Dr. Stephen Ross sailing on the Hudson River with his two Boston Terriers, one of his favorite leisure activities. In the background is the Hudson River Park's pier 40, with its 'I want to thank you' mural by Stephen Powers, an internationally recognized contemporary artist, Fulbright scholar and local resident.

When and where were you happiest? And why were so happy then?
I am most happy currently. See 'what is your current state of mind' question.

What is your greatest fear?
Despite dedicating myself to helping people with serious medical illnesses who have a fear of dying, I am very fearful of sickness and death.

What is your greatest regret?
When I was younger, I was a star athlete in soccer and baseball. In my mid-teens, I decided that I needed to focus all of my efforts on academics and felt that there was no room for anything else, and so I stopped all of my organized sports activities that I loved. I regret this decision and wish I could have balanced academics and sports at the time.

What are you most proud of?
I am most proud of the clinical care I have provided to my patients, some of whom I have treated for approximately a quarter century.

What do you consider your greatest achievement?
My greatest achievement is reducing the suffering of others through my work as a physician and researcher.

What or who is your greatest passion?
I love sailing (see Fig. 2). It reminds me a lot of research filled with endless complexities, depth, and opportunities to learn and grow. I love the euphoria and calm I get after sailing for several hours on a beautiful sunny day with great wind.

What is your favorite occupation (or activity)?
I love being a clinical psychiatrist and find the work meaningful, rewarding, humbling, and sacred.

What is your greatest extravagance?
I am a foodie and love eating amazing food, abundant in New York City, with my wife.

What is your most treasured possession?
My sailboat.

Where would you most like to live?
Besides New York City, where I have lived for the past 30 years, I would most like to live in Hawaii or Italy.

What is the quality you most admire in people?
The quality I most admire in people is kindness.

What is the trait you most dislike in people?
The trait I most dislike in people is a mix of hatred and cruelty.

What do you most value in your friends?
What I most value in my friends is the long-term bonds of mutual care and respect that we have formed, some of which I have known all of my life.

Which living person do you most admire?
My wife, Adriane Giebel, is the kindest, sweetest, most beautiful, intelligent, and loving person I know.

Who are your heroes in real life?
My parents are my heroes. I feel so lucky to have two of the most loving, supportive, and kind parents a child could ever ask for. They instilled in me the values of hard work, resilience, compassion, and service to others. My parents have been together for close to 60 years, and their love and bond have been a source of inspiration to me my entire life.

If you could have dinner with any historical figure, who would it be and why?
I love Carl Sagan because he has a special talent for explaining the complexities of astrophysics in a way that is understandable to those of us who are not astrophysicists.

Who are your favorite writers?
Sigmund Freud, Carl Jung, and Victor Frankl.

What aphorism or motto best encapsulates your life philosophy?
"Our greatest glory is not in never falling, but in rising every time we fall." — Confucius

New York City, New York, USA
30 April 2025

Stephen Ross[1]
[1]*New York University (NYU) Langone Center for Psychedelic Medicine, Bellevue Hospital Center & NYU Langone Health, NYU Neuroscience Institute, NYU Grossman School of Medicine, New York, New York 10016, USA*
✉ *e-mail: Stephen.ross@nyulangone.org*

pp.genomicpress.com

Psychedelics

OPEN

VIEWPOINT

Psychedelics in the context of stress and psychiatric disorders: A new horizon in mental health treatment

Psychedelics May 2025;1(3):14–17; doi: https://doi.org/10.61373/pp025v.0038

Keywords: Psychedelics, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, serotonin 2A receptors, stress-related psychiatric disorders

Psychiatric illness, particularly stress-related disorders including depression, anxiety and posttraumatic stress disorder, presents a considerable health burden worldwide with high prevalence, disabling symptoms, and scant efficacy of available treatments. Chronic stress is a major contributor to the origin and development of these conditions, to the detriment of both individual and, by extension, public health. More recently, psychedelics such as psilocybin, lysergic acid diethylamide, and 3,4-methylenedioxymethamphetamine (MDMA) have gained attention as potential therapeutic tools, mainly because of their ability to elicit altered states of consciousness and their impact on neuroplasticity, emotional processing, and serotonin pathways. This perspective paper discusses the mechanisms underlying the therapeutic effects of these substances, their potential utility for treating stress-related psychiatric disorders, and the need for a paradigm shift in the prevailing view of the intricate relationship between psychedelics, stress, and mental well-being.

Introduction

Stress is a natural component of human life with adaptive and dysfunctional health aspects. Whereas acute stress can improve cognitive function and initiate a cascade of physiological changes conducive for survival (1), chronic or excessive types of stress degrade the way that the brain works and disrupt mental health. It has a known risk factor for multiple mental health conditions—depression, anxiety, and posttraumatic stress disorder (PTSD), among them. Persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis with chronic stress results in extended increase in cortisol exposure which damage brain areas involved in mood regulation and memory like the hippocampus and amygdala (2). Such neurobiological disturbances contribute to the development and maintenance of psychiatric disorders and emphasize the development of creative pharmacological strategies to limit the consequences of stress.

While existing treatments such as selective serotonin reuptake inhibitors and cognitive behavioral therapy work for some, they are not universally successful. Residual symptoms or side effects affect many patients. These limitations have reignited interest in nonconventional treatments including psychedelics, in stress-related disorders.

Psychedelics, which were used in traditional religious and healing practices, captured Western medical interest in the mid-20th century as a possible treatment for alcoholism, anxiety, and depression. However, most studies were suspended after these substances were outlawed in the 1970s. Scientific developments in the field of neuroscience have contributed to renewed interest in psychedelics in recent years, particularly for their potential to support neuroplasticity and enable emotional and cognitive change. If this is the case, psychedelics may represent a new class of therapeutics, uniquely positioned to address the biological underpinnings of psychiatric disorders such as depression, PTSD, and anxiety (3). There is now a growing contingent of individuals calling for the consideration of psychedelics as medication-assisted therapies for stress-related psychiatric disorders, the subject of the present perspective paper, which will discuss where we stand based on modern psychedelic-related research, and outline what next steps may be for the field of psychedelic research in clinical psychiatry.

Neurobiological mechanisms of psychedelics in stress and psychiatric disorders

Stress-related psychiatric diseases, including depression, anxiety, and PTSD are often associated with aberrant emotional processing, including an enhanced reaction to negative stimuli, a defect in emotion regulation, and the impairment of traumatic memory processing. Long-term stress leads to a reduction in neuroplasticity, which decreases synaptic connectivity as well as cognitive and emotional flexibility. It also evokes elevated inflammation, which is implicated in the etiopathogenesis of these psychiatric disorders (4). Addressing these neurobiological changes is essential for effective treatment.

Psychedelics offer a potential in counteracting the damaging effects from prolonged exposure to stress. One of their key modes of action is to foster neuroplasticity, perhaps allowing a recovery of function of brain regions, such as the hippocampus and amygdala, that have been impacted by excessive exposure to cortisol. Through an easing of the grip of unmet emotional needs and trauma, psychedelics enable individuals to confront and integrate unsolved stressors, contributing to a more rounded form of treating mental health. While conventional treatments generally treat symptoms, psychedelic therapy treats the roots of stress-based disorders, bringing about the prospect of sustained relief. Consistent with the HPA axis signals noted above, some human trials and laboratory sessions have paired psychological change with endocrine modulation—for example, acute cortisol elevations during dosing (interpreted as state arousal/engagement) followed by normalization or improved diurnal regulation at follow-up—suggesting that stress-system recalibration may accompany therapeutic gains.

Psychedelics predominantly affect the serotonergic system in the brain, and they do so by primarily acting through serotonin 2A (5-HT_{2A}) receptors, which are highly expressed in brain areas involved in mood, emotion, and cognition, such as the prefrontal cortex (Figure 1). This receptor activation promotes neuroplasticity, functional connectivity within the brain and emotional processing that could, in turn, counteract the structural and functional damage induced by chronic stress. Preclinical studies indicate that psilocybin microdosing can upregulate brain-derived neurotrophic factor and enhance dendritic arborization in the prefrontal cortex of animal models, processes implicated in mood regulation (5). While these findings offer mechanistic insights, direct evidence in humans with alcohol use disorder remains scarce. It has been hypothesized, however, that such neuroplastic effects could contribute to

Received: 20 September 2025. Revised: 26 September 2025. Accepted: 26 September 2025.
Published online: 14 October 2025.

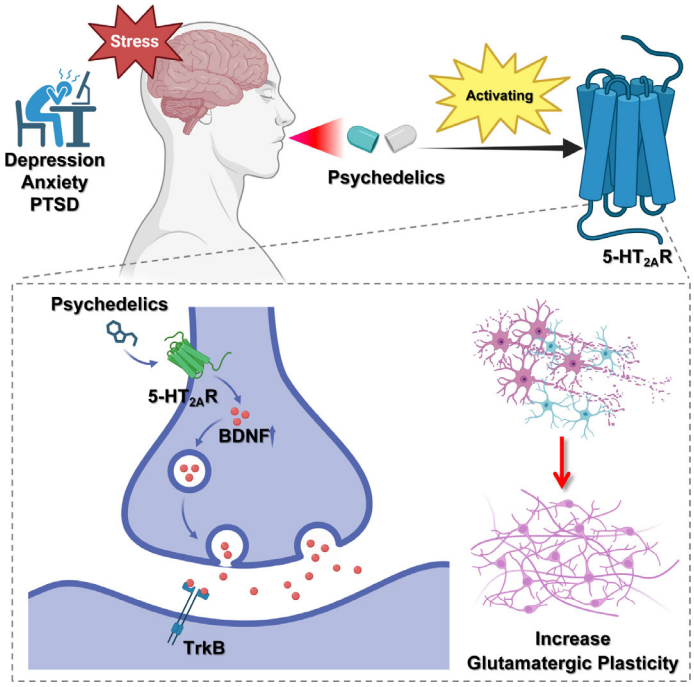


Figure 1. Psychedelics activate the 5-HT_{2A} receptor, upregulate brain-derived neurotrophic factor, and enhance synaptic plasticity, leading to therapeutic potential for stress and psychiatric disorders.

resetting maladaptive neural circuits and thereby support the sustained symptom improvements observed in some clinical trials.

Classic psychedelics, including psilocybin and lysergic acid diethylamide (LSD), also dismantle fixed, maladaptive thought patterns characteristic of disorders such as depression, anxiety, and PTSD. They accomplish this by activating 5-HT_{2A} receptors and their effects produce precisely described states of consciousness involving changes in perception, affect, and cognition. This activation of the receptor leads to decreased neuronal rigidity, enabling people to reframe experiences and learn more appropriate coping mechanisms. For example, psilocybin has been shown to decrease activity in the amygdala—a structure involved in the processing of anxiety and fear—resulting in decreased emotional reactivity to stressors and enhanced emotional regulation.

3,4-Methylenedioxymethamphetamine (MDMA) is a nonclassical (entactogenic) agent. In PTSD, its primary therapeutic signal appears to derive from acute prosociality, reduced fear reactivity, and enhanced memory reconsolidation during psychotherapy rather than from 5-HT_{2A}–driven phenomenology. Pharmacologically, it acts as a monoamine-releasing agent (serotonin $>$ dopamine $\approx$ norepinephrine) and promotes emotional openness, empathy, and decreased fear. Pharmacologically, it functions as a monoamine-releasing agent, inducing session-specific state changes that in a therapeutic context make it easier for patients to access traumatic memories without being overwhelmed, facilitating adaptive reconsolidation and reintegration. Framing MDMA-assisted therapy as a synergy between these pharmacological state effects and structured psychotherapy is critical to disrupt the vicious cycle of stress and psychiatric symptomatology and to support durable symptom improvement.

Recent evidence indicates that psychedelics may also have anti-inflammatory effects that likely contribute to the success of their therapeutic trials. For example, psilocybin has been shown to decrease proinflammatory cytokines both in preclinical and preliminary clinical studies (6). Given that psychedelics reduced inflammation, they may have additional protective benefits for the brain and body from the harmful effects of stress as they pertain to mental health. Because inflammatory tone and HPA axis function are tightly coupled, concurrent monitoring of cytokines and diurnal cortisol in future trials could clarify whether immune changes mediate, moderate, or merely accompany endocrine normalization.

In closing, the exceptional capacity of psychedelics to support neuroplasticity, improve emotion processing and decrease inflammation indicates that they might provide a new and perhaps valuable treatment for stress-related psychiatric disorders. These processes are not only critical to the symptomatic improvement of the person, but also allow the person to modify their maladaptive thought patterns and put into place new and improved mood and resilience responses to future stress exposure.

Clinical applications of psychedelics in psychiatric disorders

The therapeutic potential of psychedelics is perhaps best illustrated in the treatment of depression. Psilocybin has been studied extensively for its antidepressant effects, particularly in individuals with treatment-resistant depression. Psilocybin was administered to patients with depression who had not responded to traditional therapies (7). The results were striking: a single dose of psilocybin produced significant reductions in depressive symptoms over a period of 3 weeks, with some patients maintaining these improvements for 6 months after the treatment. Similar results have been observed in patients with anxiety associated with life-threatening illnesses, where psilocybin significantly reduced anxiety and improved quality of life. Psilocybin appears to work by reducing activity in the default mode network (DMN), a collection of brain regions that are typically overactive in individuals with depression. By quieting the DMN, psilocybin enables patients to break free from the repetitive negative thought patterns that characterize depression.

MDMA has shown remarkable promise in treating PTSD, a disorder characterized by intrusive memories, hyperarousal, and emotional numbing following trauma. In a landmark study by Mithoefer et al (8), MDMA-assisted psychotherapy significantly reduced PTSD symptoms in patients with chronic, treatment-resistant PTSD, with many experiencing long-term remission. MDMA's ability to dampen the amygdala's fear response enables patients to safely reprocess traumatic memories during therapy. A recent phase 3 clinical trial further demonstrated significant reductions in PTSD symptoms, with 67% of participants no longer meeting diagnostic criteria for PTSD after treatment (9). However, on June 4, 2024, a U.S. Food and Drug Administration (FDA) advisory committee voted overwhelmingly against approval, citing concerns over methodological limitations (e.g., challenges with blinding), variability in psychotherapy delivery, and insufficient long-term safety reporting. While this regulatory decision represents a significant hurdle, it underscores the need for more rigorous trial designs, standardized therapeutic protocols, and enhanced monitoring frameworks. Despite these challenges, MDMA remains one of the most promising novel interventions for PTSD and continues to warrant careful investigation and development.

LSD, while studied less extensively than psilocybin and MDMA, has also demonstrated potential in the treatment of anxiety and mood disorders. In a randomized, double-blind, placebo-controlled study by Gasser et al (10), patients with anxiety related to life-threatening illness received LSD-assisted psychotherapy. The study reported significant reductions in anxiety, with effects persisting for up to 12 months posttreatment. LSD's capacity to enhance emotional openness and diminish fear-based responses suggests it may be especially effective in addressing existential anxiety, a frequent challenge for patients facing terminal illness. Furthermore, the FDA has recently granted LSD a breakthrough therapy designation for the treatment of anxiety, highlighting its therapeutic promise in this area.

In addition to depression and anxiety, psychedelics have shown potential in treating other psychiatric conditions, including obsessive-compulsive disorder (OCD) and addiction. Early-phase studies involving small human samples suggest that psilocybin may alleviate OCD symptoms by disrupting the repetitive thought patterns that characterize the disorder. Similarly, psychedelics have been explored as potential treatments for substance use disorders, with promising results for reducing alcohol and nicotine dependence. These findings suggest that psychedelics may have broad applicability across a range of psychiatric disorders, particularly those involving rigid or maladaptive patterns of thought and behavior.

The therapeutic effects of psychedelics have frequently been linked to a "mystical-type experience," characterized by feelings of unity, transcendence, and a sense of interconnectedness (11). Such experiences may contribute to the therapeutic process by allowing individuals to access new insights, reframe negative thought patterns, and develop a sense of acceptance and meaning. Studies have shown that the intensity of these mystical experiences is positively correlated with the degree of symptom improvement in patients with depression and anxiety (12). Importantly, these experiences are neither necessary nor sufficient to account for clinical benefit; independent lines of evidence associate symptom improvement with enhanced cognitive and emotional flexibility and with measurable network-level neuroplastic changes (e.g., altered DMN dynamics and large-scale connectivity). Additionally, preliminary anti-inflammatory and immunomodulatory signals have been reported, and contextual factors—such as the therapeutic alliance, expectancy, and set/setting—may further shape outcomes, warranting systematic study.

Psychedelic-assisted treatments, including serotonergic agents and ketamine, can produce predictable, generally transient adverse effects such as nausea, headache, dizziness, and dissociation. Safety considerations also include cardiovascular and autonomic changes (elevations in blood pressure and heart rate), anxiety or panic in vulnerable settings, and variability in adverse event reporting across studies. Accordingly, best practice includes careful medical screening, real-time physiological monitoring, and standardized "set and setting" procedures, alongside transparent, harmonized safety reporting (13). Finally, trials in this space face well-recognized blinding and expectancy challenges due to noticeable drug effects; interpretations of efficacy should therefore incorporate strategies to mitigate and quantify expectancy (e.g., active controls and credibility checks) and report blinding integrity.

Challenges and future directions

There remain significant hurdles before psychedelics can be integrated into mainstream psychiatric practice. Chief among these is the current legal framework, which classifies most psychedelics as Schedule I controlled substances, severely restricting clinical research and therapeutic implementation. While some U.S. municipalities have moved to deprioritize enforcement of possession laws, and a few states have enacted forms of decriminalization, these measures do not equate to regulated medical access. More structured models are emerging in Oregon and Colorado, where statewide initiatives have established licensed service programs that allow supervised psilocybin use within defined therapeutic settings. As the clinical evidence base grows (14), these evolving policy experiments highlight both opportunities and challenges in making psychedelic-assisted therapies safely and responsibly accessible.

Further effort may be invested to optimize such treatments, by evaluating the most effective doses, treatment length, and patient genomes. Longitudinal studies comparing the effects of psychedelic-assisted therapy and conventional therapies for stress-related disorders are also required. Finally, larger clinical trials are necessary to validate the safety and efficacy of psychedelics over a range of psychiatric diagnoses. The development of novel psychedelic compounds that have improved safety and tolerability could overcome at least some of these limitations and improve the therapeutic efficacy of psychedelic-assisted therapy.

In addition, attempts are needed to discover and validate reliable biomarkers that can be used to enhance diagnostic accuracy and personalize treatments for stress-related psychiatric disorders (e.g., neuroimaging markers, cytokine levels, and microRNAs). The application of big data and artificial intelligence approaches could additionally lead to enhanced individualized therapeutic strategies, prediction of treatment responses, and minimization of adverse effects. To move forward in understanding stress mechanisms, promoting innovation, and translating discoveries to new therapeutic tools, interdisciplinary interaction at the levels of neuroscience, psychology, engineering, and pharmacology is required. Insights into stress-activated neural circuits and the molecular mechanisms of plasticity and receptor function may offer new targets for intervention to prevent or treat psychiatric disorders.

In order to bring these substances into the fold of mainstream psychiatry, specialized training programs for therapists will be necessary. Psychedelic therapy is qualitatively different from traditional forms of psychotherapy which rely on solely verbal interactions between the patient and doctor, in much the way that taking penicillin for a sore throat is very different from getting a throat massage. These therapists should not only have a solid understanding of psychedelic pharmacology, but also experience in working with patients through the psychedelic process, handling difficult emotions, and help in integrating these sessions into life (15).

While obstacles are significant, the promise of psychedelics to change the face of stress and psychiatric treatment is great. The profound, rapid, and sustained impact that these agents have demonstrated in numerous patients highlights their therapeutic promise for treatment-refractory or recalcitrant patients. Overcoming barriers to optimizing treatment interventions, patient screening, and safety will be critical for the clinical use of psychedelics. Their distinct modes of action as mediators of neuroplasticity, modulators of emotional plasticity, and as immune regulators unveil a fresh lens on the treatment of stress related psychiatric disorders based on the pathogenesis of these diseases.

Conclusion

Psychedelics are a potential new frontier for stress-related psychiatric disorders as they point us in a direction for treating the root cause of conditions such as depression, PTSD, and anxiety. By engaging critical neurobiological systems implicated in stress and emotion regulation, such as 5-HT_{2A} receptor activation, neuroplasticity, modulation of the DMN, and anti-inflammatory properties, psychedelics enable significant positive changes in how we process emotions, help us integrate traumas we haven't resolved, give patients different perspectives on underlying stressors, and enable the development of more adaptive coping strategies—especially when used in the context of psychotherapy. Even with obstacles, including safety, regulatory hurdles and the requirement for more, bigger clinical trials and specialized training programs for therapists, the evidence is accumulating that psychedelics could one day be a mainstay of psychiatric treatment that could change mental health care—and offer hope for patients who have not benefited from conventional therapies. There is, however, a need for continued research, and it is important to acknowledge the possible positive (and negative) side effects of these compounds, as their promise lies not only in their ability to help alleviate symptoms, but also in enabling us to gain greater insight into the human mind and to facilitate personality transformation.

Acknowledgments

We acknowledge the assistance of DeepSeek in refining and enhancing the clarity of this manuscript. DeepSeek contributed to the writing process by helping to organize ideas and improve overall readability. However, all opinions, interpretations, and conclusions presented in this work are solely those of the authors.

Author contributions

SJ, HW, and XW wrote the manuscript. XW oversaw the entire work, and supervised SJ and HW. The manuscript has been read and approved by all authors. All authors take full responsibility for all text and figure, and approve the content and submission of this work. No related work is under consideration elsewhere.

Corresponding authors: HW and XW for any aspect of the work. These corresponding authors take full responsibility for the submission process.

Funding sources

This work was supported by the Natural Science Foundation of China (T2341003; 22207103), STI2030-Major Projects [2021ZD0203000 (2021ZD0203003)] and Open Research Fund of the State Key Laboratory of Brain-Machine Intelligence, Zhejiang University (Grant No. BMI2400014).

Author disclosures

The authors declare no conflict of interest.

Sha Jin[1], Hongshuang Wang[2], and Xiaohui Wang[2,3,4]

[1]Department of Chemistry and Chemical Engineering, Hunan Institute of Science and Technology, Yueyang, 414006 Hunan, China; [2]Interdisciplinary Laboratory for Frontier Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022 Jilin, China; [3]School of Applied Chemistry and Engineering, University of Science and Technology of China, Hefei, 230026 Anhui, China; [4]State Key Laboratory of Brain Machine Intelligence, Zhejiang University, 310027 Hangzhou, China

✉ *e-mail: hongshuang.wang@ciac.ac.cn and xiaohui.wang@ciac.ac.cn*

References

1. Wang R, Zhen S, Zhou C, Yu R. Acute stress promotes brain network integration and reduces state transition variability. Proc Natl Acad Sci U S A. 2022;119:e2204144119. DOI: 10.1073/pnas.2204144119.
2. Kinlein SA, Wallace NK, Savenkova MI, Karatsoreos IN. Chronic hypothalamic-pituitary-adrenal axis disruption alters glutamate homeostasis and neural responses to stress in male C57Bl6/N mice. Neurobiol Stress. 2022;19:100466. DOI: 10.1016/j.ynstr.2022.100466. PMID: 35720261; PMCID: PMC9198473
3. Henner RL, Keshavan MS, Hill KP. Review of potential psychedelic treatments for PTSD. J Neurol Sci. 2022;439:120302. DOI: 10.1016/j.jns.2022.120302. PMID: 35700643
4. Miller MW, Lin AP, Wolf EJ, Miller DR. Oxidative stress, inflammation, and neuroprogression in chronic PTSD. Harv Rev Psychiatry. 2018;26:57–69. DOI: 10.1097/HRP.0000000000000167. PMID: 29016379; PMCID: PMC5843493
5. de Vos CMH, Mason NL, Kuypers KPC. Psychedelics and neuroplasticity: a systematic review unraveling the biological underpinnings of psychedelics. Front Psychiatry. 2021;12:724606. DOI: 10.3389/fpsyt.2021.724606. PMID: 34566723; PMCID: PMC8461007
6. Flanagan TW, Nichols CD. Psychedelics as anti-inflammatory agents. Int Rev Psychiatry. 2018;30:363–75. DOI: 10.1016/j.neuropharm.2022.109232. PMID: 36007854
7. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. N Engl J Med. 2022;387:1637–48. DOI: 10.1056/NEJMoa2206443. PMID: 36322843
8. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. J Psychopharmacol (Oxford). 2011;25:439–52. DOI: 10.1177/0269881110378371. PMID: 20643699; PMCID: PMC3122379
9. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27:1025–33. DOI: 10.1176/appi.focus.23021011. PMID: 37404971; PMCID: PMC10316215
10. Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis. 2014;202:513–20. DOI: 10.1097/NMD.0000000000000113. PMID: 24594678; PMCID: PMC4086777
11. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 2006;187:268–92. DOI: 10.1007/s00213-006-0457-5. PMID: 16826400
12. Stephen R. Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. Int Rev Psychiatry. 2018;30:317–30. DOI: 10.1080/09540261.2018.1482261. PMID: 30102082
13. Tsang VWL, Tao B, Dames S, Walsh Z, Kryskow P. Safety and tolerability of intramuscular and sublingual ketamine for psychiatric treatment in the Roots to thrive ketamine-assisted therapy program: a retrospective chart review. Ther Adv Psychopharmacol. 2023;13:20451253231171512. DOI: 10.1177/20451253231171512. PMID: 37256163; PMCID: PMC10225955
14. Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, et al.; the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. Psychedelics and psychedelic-assisted psychotherapy. Am J Psychiatry. 2020;177:391–410. DOI: 10.1176/appi.ajp.2019.19010035. PMID: 32098487
15. Phelps J. Developing guidelines and competencies for the training of psychedelic therapists. J Humanist Psychol. 2017;57(5):450–87. DOI: 10.1177/0022167817711304.

Publisher's note: Genomic Press maintains a position of impartiality and neutrality regarding territorial assertions represented in published materials and affiliations of institutional nature. As such, we will use the affiliations provided by the authors, without editing them. Such use simply reflects what the authors submitted to us and it does not indicate that Genomic Press supports any type of territorial assertions.

pp.genomicpress.com

Psychedelics

OPEN

THOUGHT LEADERS INVITED REVIEW

MDMA in Psychiatry: From PTSD to emerging indications, safety, and future directions

Ming-Ming Zhao[1], Jian-Jun Yang[1,2], and Kenji Hashimoto[1,3,4]

MDMA, 3,4-methylenedioxymethamphetamine ("ecstasy," "molly"), is a distinctive entactogen that reverses the serotonin (5-HT) transporter to increase synaptic 5-HT, while also engaging catecholaminergic and oxytocinergic pathways. In clinical trials, MDMA-assisted psychotherapy has yielded substantial improvements in treatment-resistant posttraumatic stress disorder (PTSD), although regulatory approval has been delayed over concerns about functional unblinding and protocol rigor. Early randomized, placebo-controlled studies also suggest benefits in autism spectrum disorder, eating disorders with comorbid PTSD, and anxiety related to life-threatening illness. Large epidemiological and naturalistic studies associate MDMA use with lower rates of depression, reduced suicidal ideation, and improved posttrauma coping, though causal inference is limited. MDMA-associated hyponatremia appears primarily linked to oxytocin-mediated antidiuresis (elevated plasma oxytocin without a copeptin rise), with arginine vasopressin potentially contributing under hyperthermia or polydipsia. In rodents, MDMA pretreatment enhances stress resilience and preserves adaptive neuroplasticity via a vagus-dependent gut–brain axis. This review traces MDMA's history; synthesizes evidence on acute risks (hyperthermia, hyponatremia, sympathomimetic overstimulation, and transient cognitive effects); and evaluates long-term outcomes and putative resilience mechanisms. Future work should standardize dosing and psychotherapeutic protocols, incorporate biomarkers to guide patient selection, and conduct adequately powered trials across emerging indications, alongside long-term safety monitoring and multidisciplinary collaboration.

Psychedelics May 2025;1(3):18–28; doi: https://doi.org/10.61373/pp025i.0035

Keywords: Entactogen, gut–brain axis, MDMA, oxytocin, resilience, serotonin

Introduction

MDMA (3,4-methylenedioxymethamphetamine), commonly known as ecstasy or molly, is a derivative of psychostimulant methamphetamine first synthesized by Merck chemist Anton Köllisch in 1912 as an "anorectic" under the names "Methylsafrylamin" and "Safrylmethylamin" (Figures 1 and 2) (1, 2). It is widely classified as an entactogen, reflecting its potent empathogenic effects in humans. Although Merck never developed it beyond a chemical precursor, Alexander Shulgin rediscovered its unique psychoactive effects in the 1970s (Figure 2). In the late 1970s and early 1980s, several psychotherapists began using MDMA to augment talk therapy (3). Early open-label pilot studies—most notably by Greer and Tolbert—reported pronounced and lasting improvements in mood, social functioning, and insight following a single MDMA-assisted session (3, 4).

By the mid-1980s, rising recreational use and concerns about neurotoxicity and dependence led to MDMA's classification as a Schedule I substance in 1985, effectively halting clinical research (Figure 2). Interest reemerged in the early 2000s when pilot trials demonstrated that MDMA-assisted psychotherapy could benefit treatment-resistant posttraumatic stress disorder (PTSD), prompting the Food and Drug Administration (FDA) to grant Breakthrough Therapy designation in August 2017 (Figure 2). Since then, controlled trials have investigated optimal dosing, safety profiles, and mechanisms of action, positioning MDMA as a potential paradigm shift in psychiatric treatment (5, 6).

Unlike classical stimulants, MDMA enhances monoaminergic transmission—particularly serotonin (5-HT) release—and stimulates oxytocin secretion, producing empathogenic effects such as increased sociability, emotional openness, and reduced fear responses (7–9). These interoceptive effects distinguish MDMA from both psychostimulants and classical hallucinogens. Today's research sits at the intersection of neuroscience, psychopharmacology, and psychotherapy, with ongoing studies clarifying long-term safety, refining therapeutic protocols, and exploring applications beyond PTSD—including autism spectrum disorder (ASD), eating disorders (EDs), depression, social anxiety, and substance use disorders (10).

This review traces MDMA's journey—from its chemical origins and early clinical promise through prohibition and resurgence—to summarize current evidence, highlight unresolved questions, and outline future directions for harnessing its therapeutic potential.

Pharmacology of MDMA

Serotonin and catecholamine systems

MDMA's primary action is to reverse the serotonin transporter (SERT), causing a massive efflux of 5-HT into the synaptic cleft that underlies its acute mood elevation, anxiolysis, and prosocial (empathogenic) effects (11–13). In rodents, genetic or pharmacological blockade of SERT or 5-HT_{1B} receptors in the nucleus accumbens (NAc) abolishes MDMA-induced social affiliation, whereas its rewarding (reinforcing) effects depend on dopaminergic signaling (14, 15). The new study shows that MDMA's strong 5-HT release in the NAc actively restrains its own dopamine (DA)-mediated reinforcement, helping explain why MDMA has lower abuse liability than methamphetamine despite similar DA-releasing capacity (16). In mice, NAc DA release scaled with conditioned place preference (CPP); knocking out SERT (or locally blocking SERT with escitalopram) or antagonizing 5-HT_{2C} receptors each boosted DA release and shifted CPP leftward, indicating that 5-HT tone in the NAc suppresses reinforcement. By contrast, blocking 5-HT_{1B} receptors—which mediate MDMA's prosocial effects—did not enhance reinforcement, suggesting distinct circuits for prosocial versus abuse-linked actions. Using this assay platform, (*R*)-MDMA is predicted to retain prosocial effects with low abuse potential.

Both systemic MDMA and direct optogenetic stimulation of NAc 5-HT inputs rescue social and empathy-like deficits in multiple ASD models, highlighting NAc 5-HT as a core mediator of its empathogenic profile

[1]Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, 450052 Zhengzhou, China; [2]Department of Anesthesiology, The First Affiliated Hospital of Nanjing Medical University, 210029 Nanjing, China; [3]Chiba University Center for Forensic Mental Health, 260-8670 Chiba, Japan; [4]Basic Medicine Research Innovation Center for Cardiometabolic Diseases, Ministry of Education, Southwest Medical University, 646000 Luzhou, Sichuan, China.
Corresponding Authors: Jian-Jun Yang. E-mail: yjyangjj@126.com at Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, and Kenji Hashimoto. E-mail: hashimoto@faculty.chiba-u.jp at Chiba University Center for Forensic Mental Health, Chiba, Japan.
Received: 20 June 2025. Revised: 25 September 2025. Accepted: 26 September 2025.
Published online: 14 October 2025.

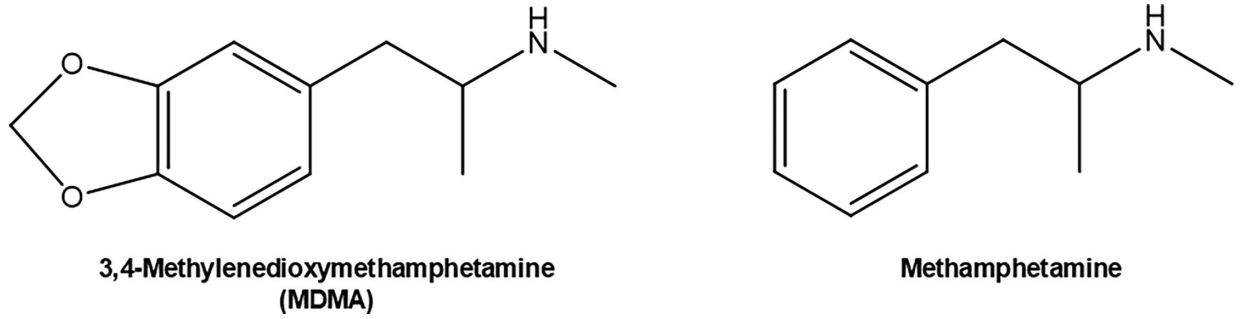


Figure 1. Chemical structures of MDMA and methamphetamine. Structures of 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) and *N*-methylamphetamine (methamphetamine), illustrating their shared phenethylamine core and highlighting MDMA's unique 3,4-methylenedioxy bridge.

(17, 18). Using dynamic [^{11}C]DASB positron emission tomography (PET), Ionescu et al. (19) revealed clear changes in molecular connectivity after a single dose of MDMA in rats, establishing a direct link between SERT occupancy and alterations in the functional brain network.

In human volunteers, pretreatment with selective serotonin reuptake inhibitors such as citalopram markedly blunts MDMA's subjective "entactogenic" and cardiovascular effects (20–22), and the 5-HT$_{2A}$ receptor antagonist ketanserin selectively reduces its perceptual changes and emotional excitation (22). Together, these findings confirm that 5-HT release is both necessary and largely sufficient for MDMA's psychoactive effects.

Beyond 5-HT, MDMA acts as a releaser and reuptake inhibitor of norepinephrine—and to a lesser extent DA—fueling its sympathomimetic, stimulant, and reinforcing properties (23, 24). It also binds multiple receptors (5-HT$_{1A}$/$_{1B}$/$_{2A}$, M$_1$ muscarinic, H$_1$ histamine, α/β-adrenergic, and DA receptors), enriching its subjective and physiological profile. Microdialysis studies in mice demonstrate that MDMA elevates striatal DA via both DAT (DA transporter) and SERT, since increases are abolished only in DAT/SERT double knockouts (25).

Finally, MDMA provokes robust neuroendocrine responses: chronic users show 100%–200% higher basal cortisol (26), while acute "dancefloor" exposures can spike cortisol up to 800% (27). Transient prolactin surges and inappropriate vasopressin release also occur, occasionally precipitating hyponatremia (Figure 3) (28–32).

Oxytocin system and hypothalamic–pituitary–adrenal axis

Oxytocin is a hypothalamic peptide hormone and neuromodulator that promotes social bonding, trust, and prosocial behaviors by acting on limbic and reward circuits. It also modulates stress and anxiety responses, dampening the hypothalamic–pituitary–adrenal (HPA) axis and exerting anti-inflammatory effects (33–36). MDMA powerfully engages the oxytocin system, a key mediator of social bonding, trust, and empathy. In humans, a single oral dose produces rapid plasma oxytocin rises at 90–120 min that correlate more strongly with sociability and closeness than with blood MDMA levels (37–40). Genetic variation in the *OXTR* gene (rs53576) further modulates the prosocial effects of MDMA in humans (41).

Enantiomer-specific studies reveal that (*S*)-MDMA (125 mg) elicits greater stimulant-like subjective effects, cardiovascular activation, and elevations in prolactin, cortisol, and oxytocin than (*R*)-MDMA or the racemate, underscoring distinct pharmacological profiles (42). Neurophysin I, a stable surrogate for oxytocin, rises 20-fold after MDMA in healthy controls but not in patients with hypothalamic–pituitary dysfunction, validating its use as a biomarker and linking oxytocin surges to euphoria, trust, and fear reduction (43).

Additionally, a single 100 mg dose of MDMA in healthy control subjects stimulated the HPA axis, producing significant increases in plasma adrenocorticotropic hormone levels from baseline to 120 min (44). This was accompanied by a significant rise in cortisol levels. In contrast, MDMA did not alter levels of thyroid-stimulating hormone, luteinizing hormone, prolactin, growth hormone, free thyroxine, testosterone, or estradiol. These findings suggest that MDMA strongly activates the HPA axis in humans.

In rodents, MDMA activates oxytocin neurons in the paraventricular and supraoptic nuclei of the hypothalamus via 5-HT$_{1A}$ receptor stimulation—effects that, along with associated social behaviors, are blocked by the 5-HT$_{1A}$ antagonist WAY-100635 (45, 46). Drug-discrimination studies further show that the oxytocin analog carbetocin partially substitutes for MDMA's subjective cue, whereas the oxytocin antagonist atosiban disrupts MDMA-appropriate responding, underscoring oxytocin receptor activation as a key interoceptive component of its prosocial effects (47).

In a PTSD model, Avgana et al. (48) demonstrated that microinjecting MDMA into the medial prefrontal cortex (mPFC) of male rats enhanced fear extinction and reversed both the shock-induced increase in

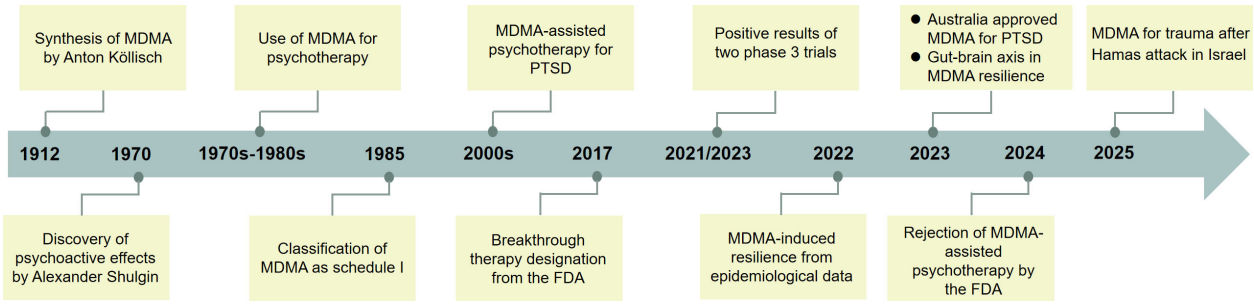


Figure 2. Timeline of MDMA's development and clinical research milestones. A chronological overview of pivotal events: (1) First synthesis of MDMA in 1912. (2) Rediscovery and early psychotherapeutic applications in the 1970s-1980s. (3) Drug Enforcement Administration (DEA) classifies MDMA as a Schedule I substance in 1985. (4) Launch of Phase I safety trials for MDMA-assisted psychotherapy in the early 2000s. (5) FDA grants Breakthrough Therapy Designation in 2017. (6) Publication of positive phase III trial results in 2021 and 2023. (7) FDA issues a non-approval decision for MDMA-assisted psychotherapy. (8) Emerging evidence of MDMA-induced resilience in humans and rodent studies from 2022. (9) Australia's Therapeutic Goods Administration approved MDMA for PTSD under Schedule 8, and key findings of gut–brain axis in MDMA resilience in 2023. (10) Ongoing controlled trials in PTSD, ASD, and EDs. Each milestone is annotated with the year and a brief descriptor of its impact on MDMA's therapeutic trajectory.

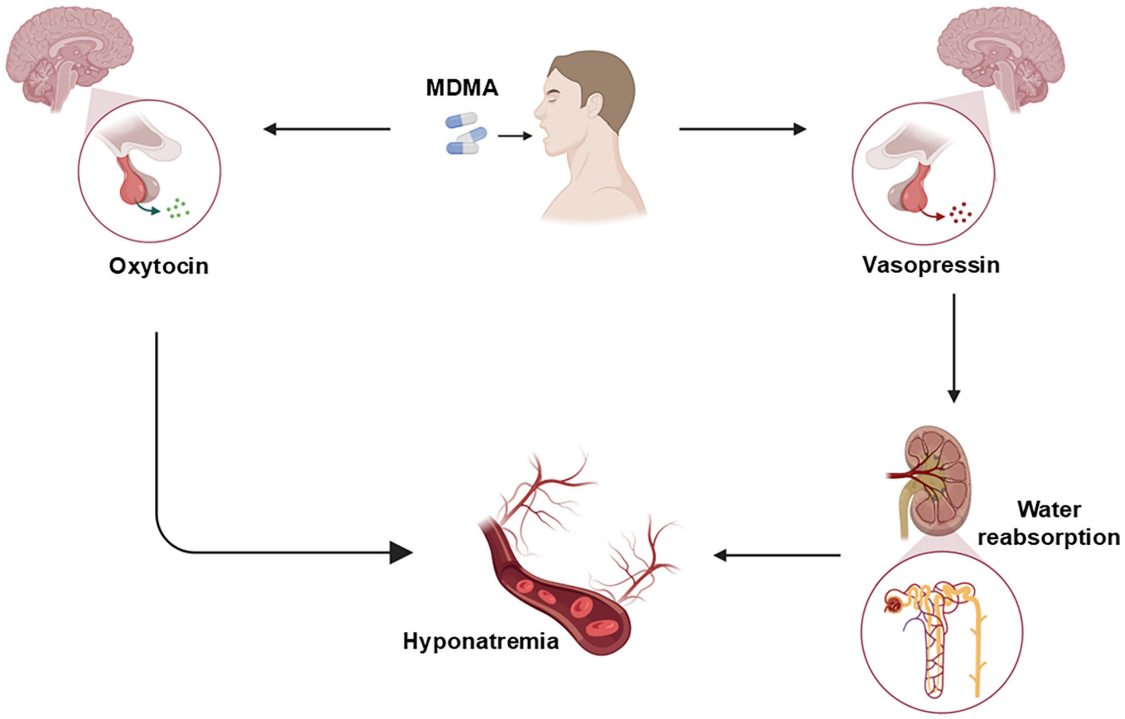


Figure 3. Mechanisms of MDMA-induced dilutional hyponatremia. MDMA acutely increases synaptic serotonin, promoting antidiuresis through two pathways. Primary evidence indicates an oxytocin-mediated effect: plasma oxytocin rises ~4- to 5-fold without a concomitant increase in copeptin (a vasopressin precursor fragment), consistent with enhanced free-water reabsorption. In parallel, nonosmotic vasopressin (ADH) release may contribute under heat stress, hyperthermia, or excessive water intake. Both pathways increase aquaporin-2 insertion in renal collecting ducts, reducing free-water clearance. When combined with high fluid intake, plasma becomes diluted and serum sodium falls, producing hyponatremia. Controlled trials show an average ~3 mEq/L sodium reduction and ~31% hyponatremia incidence with unrestricted fluids; fluid restriction mitigates risk. This illustration was created using BioRender.com.

freezing and deficits in social behavior. Shock exposure disrupted oxytocin receptor gene expression and triggered neuroinflammation in the mPFC and basolateral amygdala; MDMA treatment normalized these alterations. Importantly, the oxytocin receptor antagonist L-368,899 abolished MDMA's beneficial effects on extinction and freezing. Together, these findings suggest that MDMA's therapeutic actions in this PTSD model depend on modulating oxytocin receptor expression and neuroinflammatory processes, with oxytocinergic signaling mediating its impact on extinction and anxiety.

Vagus nerve plays a role in the communication between the brain and peripheral organs including gastrointestinal tracts (49–52). Finally, subdiaphragmatic vagotomy in rats drastically reduces both baseline and MDMA-induced oxytocin release and c-Fos activation in hypothalamic nuclei, demonstrating the vagus nerve's critical role in gut–brain mediation of MDMA's oxytocinergic effects (53).

Other systems

MDMA also modulates glutamatergic neurotransmission. It triggers a rapid extracellular glutamate surge in the dentate gyrus via 5-HT_{2A} receptor activation, causing parvalbumin interneuron loss that is prevented by *N*-methyl-D-aspartate receptor (NMDAR) antagonists (MK-801) or selective 5-HT_{2A} blockade (MDL100907) (54). Both NMDAR and AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor) contribute to MDMA's modulation of social defeat stress in mice (55).

In summary, MDMA's multifaceted pharmacology—spanning monoamines, neuroendocrine hormones, the oxytocin system, and glutamatergic circuits—underpins its distinctive therapeutic profile and highlights diverse targets for probing its clinical benefits and potential risks.

Adverse events of MDMA

Hyperthermia and hyponatremia are the most significant acute adverse effects of MDMA use. MDMA can cause dangerous elevations in body temperature and dilute blood sodium—even when taken alone—and these risks are amplified by vigorous activity and excessive fluid intake (Table 1) (24, 56–59). Sympathomimetic overstimulation produces tachycardia, hypertension, sweating, jaw clenching (bruxism), nausea, and blurred vision (Figure 4). In severe cases, this overstimulation can progress to serotonin syndrome, rhabdomyolysis, acute liver injury, multiorgan failure, or sudden death (Figure 4). Headache, difficulty concentrating, insomnia, and fatigue frequently occur in the hours to days following MDMA ingestion (Table 1) (60, 61).

Acute hyponatremia is a potentially serious complication after even a single dose of MDMA. Across four placebo-controlled crossover trials (100–125 mg), MDMA lowered plasma sodium by ~3 mEq/L; with unrestricted fluids, ~31% developed hyponatremia. Concurrently, plasma oxytocin rose ~4- to 5-fold without an accompanying increase in copeptin (a vasopressin precursor fragment), implicating oxytocin-mediated antidiuresis as the principal mechanism. Arginine vasopressin (ADH) cannot be excluded under heat stress, hyperthermia, or excessive water intake, where nonosmotic ADH release may occur. Importantly, fluid restriction mitigated this risk (Figure 3) (62).

A recent study by Rana et al. (63) demonstrated that bile acids and the gut microbiota contribute to MDMA-induced hyperthermia. A single injection of MDMA (20 mg/kg) altered serum levels of primary unconjugated bile acids (cholic acid and chenodeoxycholic acid) and the secondary bile acid deoxycholic acid in control rats. Five days of microbiome depletion—via vancomycin, bacitracin, and neomycin in the drinking water—abolished these bile acids and converted MDMA's hyperthermic effect into a hypothermic response. These findings suggest that gut microbiota-derived bile acids are key mediators of MDMA-induced hyperthermia (Figure 4) (63).

Heavy, prolonged recreational MDMA use has been linked to persistent sleep disturbances, depressed mood, anxiety, impulsivity, and hostility. Cognitive deficits—particularly in episodic memory, working memory,

Table 1. Adverse events in humans after acute and chronic treatment of MDMA (3,4-methylenedioxymethamphetamine)

Acute adverse events of MDMA[a]	Symptoms
Cardiovascular effects	Tachycardia, hypertension, and, less frequently, arrhythmias or chest pain
Thermoregulatory disturbances	Hyperthermia or, paradoxically, hyponatremia due to inappropriate vasopressin release and excessive water intake
Neuropsychiatric and somatic symptoms	Anxiety, agitation, confusion, jaw clenching (bruxism), nausea, headache, sweating, and, in rare cases, serotonin syndrome
Adverse events with chronic MDMA use	**Symptoms**
Cognitive and mood disturbances	Persistent memory impairments, deficits in attention and executive function, as well as increased risk of depression and anxiety during withdrawal
Neurotoxicity indicators	Evidence of long-term serotonergic axon damage and reduced serotonin transporter density on neuroimaging
Other health issues	Sleep disorders, dental problems (from bruxism), potential liver strain, and the development of substance-use disorder patterns

[a]3,4-methylenedioxymethamphetamine.

and attention—may last 6 months or longer after cessation (Table 1) (59, 64).

Neurotoxicity in the brain of MDMA users

Human neuroimaging and cognitive findings

PET studies in abstinent MDMA users consistently show reduced SERT availability throughout cortical and subcortical regions, alongside compensatory upregulation of postsynaptic 5–HT_{2A} receptors (65–68). These parallel presynaptic and postsynaptic changes suggest serotonergic terminal damage may underlie the mood, cognitive, and impulse-control disturbances observed in chronic users. Structural magnetic resonance imaging (MRI) further reveals hippocampal volume losses and cortical thinning (notably in orbitofrontal and parietal areas), while diffusion- and functional-MRI studies document white-matter microstructural alterations and aberrant activation during memory and attention tasks (69, 70). Neuropsychological testing corroborates these imaging findings, showing deficits in verbal/visual memory, sustained attention, and executive function that often correlate with individual SERT reductions (71). However, variability in polydrug exposure and abstinence duration underscores the need for longitudinal, controlled studies to distinguish lasting neurotoxicity from reversible neuroadaptations.

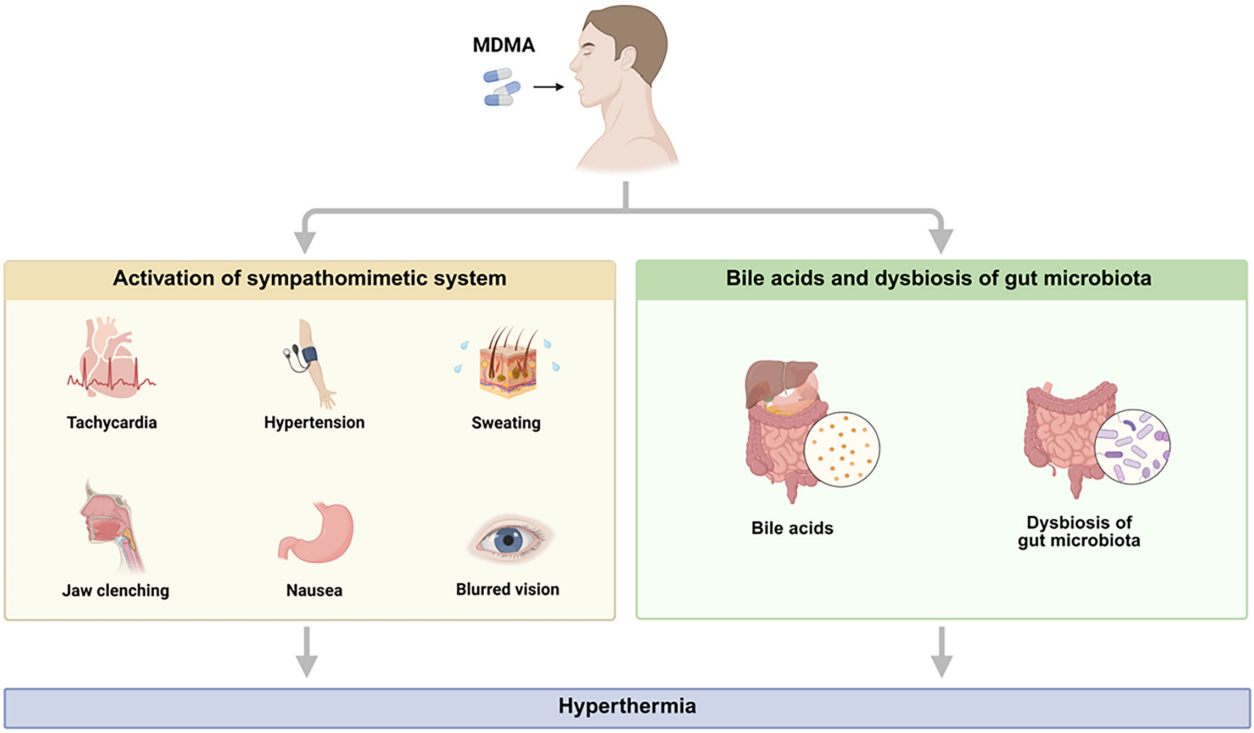


Figure 4. Sympathetic activation and thermoregulatory dysregulation in MDMA-induced hyperthermia. MDMA acutely elevates central monoamines (serotonin, norepinephrine, and dopamine), producing sympathetic hyperactivation that increases heart rate and blood pressure, induces peripheral vasoconstriction, and amplifies muscle activity (e.g., jaw clenching and tremor), thereby raising metabolic heat production. Concurrent thermoregulatory impairment—including reduced sweating and cutaneous heat loss—combined with environmental/behavioral stressors (crowded, warm venues; prolonged exertion) limits heat dissipation and precipitates hyperthermia. Emerging evidence also links MDMA to gut microbiota dysbiosis and altered bile acid profiles, which may further influence thermogenesis and heat clearance. This illustration was created using BioRender.com.

Preclinical rodent studies

In rodent models, high-dose MDMA triggers an acute phase of massive 5-HT depletion and tryptophan-hydroxylase inactivation, followed by a delayed, sustained reduction in tissue 5-HT levels, SERT binding, and synthetic-enzyme activity lasting months (11, 72–76). Histology reveals swollen, fragmented ("dystrophic") serotonin axons—especially from the dorsal raphe—consistent with distal axotomy without cell-body loss (77). MDMA-induced hyperthermia exacerbates oxidative stress and free-radical formation, and interventions that lower core temperature or scavenge radicals attenuate these serotonergic injuries (78).

Nonhuman primate studies

Squirrel monkeys and macaques display a similar but more protracted neurotoxic profile: forebrain 5-HT depletions and SERT losses persist for years, and histopathology shows argyrophilic axonal degeneration and microglial activation within serotonergic projection areas—while dopaminergic and other monoaminergic systems remain relatively intact (79–82).

Together, human imaging and behavioral data, rodent models, and primate studies converge to demonstrate that MDMA selectively injures serotonergic nerve terminals via mechanisms amplified by hyperthermia and oxidative stress. These findings have critical implications for balancing MDMA's therapeutic promise against its potential for long-term neurotoxicity.

MDMA-assisted psychotherapy

Posttraumatic stress disorder

Renewed interest in MDMA-assisted psychotherapy began in 1986 when Rick Doblin founded the Multidisciplinary Association for Psychedelic Studies (MAPS) to explore its therapeutic potential. Early Phase I safety trials around 2000 paved the way for Phase II work: the first randomized, controlled trial in 2010 treated 20 patients with treatment-refractory PTSD, reporting an 80% remission rate that persisted at 3 years (83, 84). A subsequent double-blind Phase II trial in military veterans showed that MDMA doses of 75 mg and 125 mg yielded significantly greater reductions in PTSD symptom severity than a low-dose (30 mg) comparator (85).

In August 2017, the FDA granted Breakthrough Therapy designation to MDMA-assisted psychotherapy, accelerating its clinical development (Figure 2). MAPS Public Benefit Corporation (now Lykos Therapeutics) completed two pivotal Phase III trials (86, 87) in December 2023 and submitted a New Drug Application; however, in August 2024 the FDA requested an additional Phase III study, citing concerns over trial conduct and data integrity (88, 89). Table 2 summarizes the frequencies of treatment-emergent adverse events (TEAEs) from two clinical trials (88, 89). Most participants experienced at least one TEAE during the studies. No serious TEAEs were reported. The most frequently reported TEAEs were muscle tightness, nausea, decreased appetite, and hyperhidrosis.

Australia's Therapeutic Goods Administration reclassified MDMA and psilocybin to Schedule 8, effective July 1, 2023, permitting trained psychiatrists to prescribe them alongside psychotherapy under ethics-committee oversight (Figure 2) (90–92). Critics argue this move is premature given the lack of standardized treatment protocols and limited high-quality evidence on real-world safety and efficacy. Recent systematic reviews report symptom, response, and remission benefits for PTSD, but rate the certainty of efficacy as low to very low due to bias, small samples, and short follow-up; safety conclusions remain constrained by inconsistent adverse event reporting (93). Future work must rigorously assess study bias, therapy protocols, dosing regimens, and long-term outcomes to inform clinical adoption.

When the FDA ultimately rejected the application, it highlighted pervasive functional unblinding—90% of active-drug and 75% of placebo participants correctly guessed their assignment—and inadequately defined psychotherapeutic protocols. Serious safety and data-integrity issues (including under-reported adverse events, compromised informed consent, mishandled sexual-misconduct allegations, and missing abuse-liability data) further undermined the submission (94). In draft guidance, the FDA recommended more rigorous blinding strategies (e.g., low-dose comparators) and clearer metrics for evaluating therapy's contribution to outcomes. Despite this setback, MDMA-assisted psychotherapy remains one of the most promising treatments for refractory PTSD; the field must now establish consensus on acceptable unblinding thresholds, standardized therapy protocols, and integrated trial designs that combine drug and psychotherapeutic elements (94).

Table 2. Adverse events in clinical trials of MDMA (3,4-methylenedioxymethamphetamine) for PTSD (posttraumatic stress disorder) (Mitchell et al. 2021 and 2023)

Adverse event	MDMA[a] (n = 46)	Placebo (n = 44)
Muscle tightness	29 (63.0%)	5 (11.4%)
Decreased appetite	24 (52.2%)	5 (11.4%)
Nausea	14 (30.4%)	5 (11.4%)
Hyperhidrosis	9 (19.6%)	1 (2.3%)
Feeling cold	9 (19.6%)	3 (6.8%)
Restlessness	7 (15.2%)	0
Mydriasis	7 (15.2%)	0
Adverse event	**MDMA (n = 53)**	**Placebo (n = 51)**
Muscle tightness	31 (58.5%)	13 (25.5%)
Nausea	24 (45.3%)	11 (21.6%)
Nausea	19 (35.8%)	5 (9.8%)
Hyperhidrosis	18 (34.0%)	3 (5.9%)
Feeling hot	14 (26.4%)	6 (11.8%)
Feeling cold	11 (20.8%)	3 (5.9%)
Paresthesia	10 (18.9%)	1 (2.0%)
Chest discomfort	9 (17.0%)	2 (3.9%)
Dry mouth	9 (17%)	4 (7.8%)
Chills	8 (15.1%)	1 (2.0%)
Feeling jittery	8 (15.1%)	0
Restlessness	8 (15.1%)	2 (3.9%)
Vision blurred	8 (15.1%)	0

[a] PTSD: posttraumatic stress disorder

NOTE: The most common treatment-emergent adverse events with incidence >15%. From the data of Mitchell et al. (86, 87).

In a double-blind, placebo-controlled crossover trial in 16 adults with subthreshold PTSD symptoms, participants were first stratified by baseline nonconscious threat-evoked functional magnetic resonance imaging (fMRI) responses into high ($NTNA^+$) and low ($NTNA^-$) amygdala reactivity groups (95). After 120 mg MDMA versus placebo, only the $NTNA^+$ subgroup showed acute normalization of negative-affect circuitry—marked by significant reductions in amygdala and subgenual anterior cingulate cortex (sgACC) activity, enhanced sgACC–amygdala connectivity, and greater likability of threat expressions. These findings demonstrate that pre-treatment neural profiling can predict MDMA's capacity to modulate threat processing, suggesting neuroimaging biomarkers may guide personalized MDMA-assisted therapies (95).

Autism spectrum disorder

Individuals with ASD often struggle with nonverbal communication—eye contact, facial expressions, and gestures—and pragmatic language, which impairs reciprocal social interaction (96). MDMA's entactogenic profile—emotional openness, reduced social fear, and enhanced empathy—suggests therapeutic potential in ASD (97–100). In a randomized, double-blind, placebo-controlled trial, adults with ASD who received MDMA-assisted psychotherapy showed significant reductions in social anxiety compared with placebo, as measured by the Liebowitz Social Anxiety Scale (primary endpoint) (101). Since MDMA drives oxytocin release, which may ameliorate social deficits in ASD, larger studies are needed to confirm its safety and efficacy in this population.

Eating disorders

Individuals with EDs often experience social withdrawal, heightened social anxiety, and impaired social cognition—such as difficulty interpreting others' emotions and intentions—which can erode their support networks (102, 103). MDMA-assisted psychotherapy offers reduced fear, self-criticism, and increased compassion, trust, and sociability (104), making

it a promising intervention for patients with ED, especially those with comorbid PTSD. In a randomized, placebo-controlled trial of patients with severe PTSD and comorbid eating pathology, MDMA-assisted therapy significantly reduced ED symptoms (105). The primary endpoint was CAPS-5, with ED measures as secondary endpoints. While encouraging, these findings require confirmation in larger, well-powered trials to establish efficacy and safety in ED populations.

Life-threatening illness

Depression, anxiety, and existential distress are common in patients with life-threatening illnesses and can undermine quality of life and treatment adherence (106). Early clinical work indicates that MDMA-assisted psychotherapy may relieve this psychological burden (107–110). In a Phase II Australian trial, up to 32 individuals with stage III–IV cancer were randomized to receive MDMA-augmented therapy versus placebo, with primary endpoints of anxiety, depression, and quality of life. In a double-blind cohort of 18 patients, those in the MDMA group (two 8-h sessions at 125 mg) experienced a mean 23.5-point reduction in State-Trait Anxiety Inventory scores 1-month posttreatment—compared to an 8.8-point reduction in the placebo group—with benefits sustained at 6 and 12 months following crossover sessions (111). Earlier pilot data in mixed cancer and neurological disease cohorts also demonstrated significant improvements in anxiety, depression, and sleep quality. These promising results underscore the need for larger, controlled trials to establish MDMA's efficacy and safety in relieving distress associated with life-threatening illnesses.

MDMA as a resilience enhancer

Epidemiological evidence

In a 2008–2019 sample of 484,732 U.S. adults, lifetime MDMA/ecstasy use was linked to lower odds of past-year suicidal thinking and planning, while psilocybin use was associated with reduced risk of past-month psychological distress and suicidal thoughts; by contrast, LSD use showed a modest increase in suicidal thinking (112). Similarly, analysis of 213,437 adults found that lifetime MDMA/ecstasy and psilocybin users had significantly lower odds of lifetime and past-year severe major depressive episodes, whereas other substances conferred no protection (113). In a nationally representative cohort of 241,675 adults (2015–2020), MDMA (ecstasy/molly) use corresponded with reduced rates of serious psychological distress, depression, and suicidal ideation (114). Together, these observational data suggest that MDMA and psilocybin use correlates with lower depression and suicidality, underscoring the need for controlled trials to establish causality.

Naturalistic trauma study in israel

On the morning of October 7, 2023, around 3500 festivalgoers at Israel's Nova event—many of whom were under the influence of MDMA or LSD—were caught in a Hamas gun attack that killed hundreds. Researchers at the University of Haifa followed more than 650 trauma survivors, about two-thirds of whom had used recreational drugs. Primary outcomes included the PTSD Checklist for DSM-5 (PCL-5; cutoff $\geq$ 33) and the Kessler Psychological Distress Scale (K6; cutoff $\geq$ 13). Survivors who had used MDMA alone showed notably better psychological outcomes over the critical 5 months posttrauma—improved sleep quality, lower distress, stronger social bonding, and greater openness to support (115). The authors attribute these benefits to MDMA's enhancement of prosocial hormones like oxytocin and its promotion of neural plasticity, despite ongoing legal and ethical challenges.

Although these observational studies suggest that MDMA and classic psychedelics may foster resilience, causality cannot be established. Unmeasured factors—such as baseline personality traits, social support networks, or self-selection into surveys—could partially explain the associations. Longitudinal, prospective research is needed to disentangle drug effects from pre-existing individual differences and to elucidate the mechanisms underlying these epidemiological observations.

Gut–brain axis and oxytocin-mediated mechanisms

Approximately 90% of the body's 5-HT is synthesized by enterochromaffin cells in the gastrointestinal mucosa, where it regulates intestinal motility, secretion, and blood flow (116–118). Beyond local effects, gut-derived 5-HT signals to the enteric and central nervous systems—via neural pathways and the circulation—modulating appetite, mood, and overall gut–brain communication (52). Preclinical studies in rodents have demonstrated that MDMA can promote stress resilience across multiple paradigms. Pretreatment with MDMA did not produce systemic inflammation and depression-like behaviors in mice exposed to chronic social defeat stress (CSDS) (119) or chronic restraint stress (CRS) models (120). In the CSDS paradigm, repeated MDMA administration preserved sucrose preference, normalized splenomegaly, and prevented stress-induced shifts in gut microbiota composition—findings that link MDMA's prophylactic effects to modulation of the microbiota–brain axis. In a CRS model, daily MDMA pretreatment (10 mg/kg for 14 days) prevented the onset of anhedonia-like behavior and restored levels of synaptic proteins and BDNF in the prefrontal cortex—effects that were abolished by subdiaphragmatic vagotomy, implicating a critical role for the gut–brain axis via the vagus nerve in MDMA's resilience-enhancing actions (120).

Repeated intermittent MDMA administration (10 mg/kg, three times weekly for 6 weeks) significantly reduced demyelination in the corpus callosum of cuprizone-treated mice (121). Gut microbiota and nontargeted metabolomics analyses revealed notable differences in specific gut bacteria and plasma (β-D-allose and L-sorbose) or fecal metabolite (carnitine) levels between MDMA-treated and vehicle-treated cuprizone-exposed mice. Negative correlations were found between the levels of metabolites (β-D-allose, L-sorbose, and carnitine) and the relative abundance of *Romboutsia* and *Romboutsia timonensis*. These findings suggest that intermittent MDMA administration may alleviate brain demyelination of cuprizone-treated mice via the gut–brain axis (121). Moreover, repeated intermittent MDMA administration (10 mg/kg, three times weekly for 6 weeks) significantly reduced bone mineral density of ovariectomized female through a gut–microbiota–bone axis (122).

Additionally, repeated oral MDMA administration to male rats caused significant changes in the gut microbiota across these regions (small intestine, cecum, and colon), with distinct effects observed in each (123). Untargeted metabolomics analysis revealed that MDMA significantly altered levels of two metabolites-ferulic acid and methylmalonic acid-in the colon, without changes in the blood, small intestine, or cecum. Notably, methylmalonic acid levels in the colon positively correlated with *Lawsonibacter* and *Oscillibacter*. These findings suggest that repeated oral MDMA treatment can alter gut microbiota composition across intestinal regions, potentially contributing to its pharmacological effects (123).

In addition, MDMA triggers the release of oxytocin—a hormone that enhances social bonding, trust, and emotional openness—which likely contributes to its therapeutic benefits by reducing stress and facilitating trauma processing (28, 37). Oxytocin is synthesized in the hypothalamus, particularly in the paraventricular and supraoptic nuclei, and is released via the posterior pituitary to regulate social bonding, stress responses, and emotional behaviors. Recent research has revealed that the human intestinal epithelium produces oxytocin and that *Limosilactobacillus reuteri* promotes its secretion via secretin from enteroendocrine cells, thereby identifying oxytocin as an intestinal hormone and revealing a mechanism by which gut microbes enhance host health (124). Furthermore, another study demonstrated that the subdiaphragmatic vagus nerve is critical for MDMA's effects on the oxytocin system in rats, as subdiaphragmatic vagotomy significantly reduced both baseline and MDMA-induced increases in plasma and hypothalamic oxytocin levels (53). Collectively, these findings suggest that brain–body communication via the vagus nerve plays a key role in MDMA-induced resilience (Figure 5).

Conclusion and future perspectives

MDMA's unique pharmacology—marked by robust 5-HT and oxytocin release, engagement of the HPA axis, and modulation of glutamatergic circuits—underlies its rapid and potent psychological effects (125, 126). These actions converge on limbic and reward pathways to foster emotional openness, reduced fear, and enhanced social cognition. Preclinical and early-phase clinical data collectively demonstrate that MDMA can both acutely alleviate distress and, with repeated dosing, confer durable resilience to stressors via vagus nerve-mediated gut–brain axis.

Clinical evidence in treatment-resistant PTSD is the most mature, with Phase II and III trials showing high remission rates and durable benefits

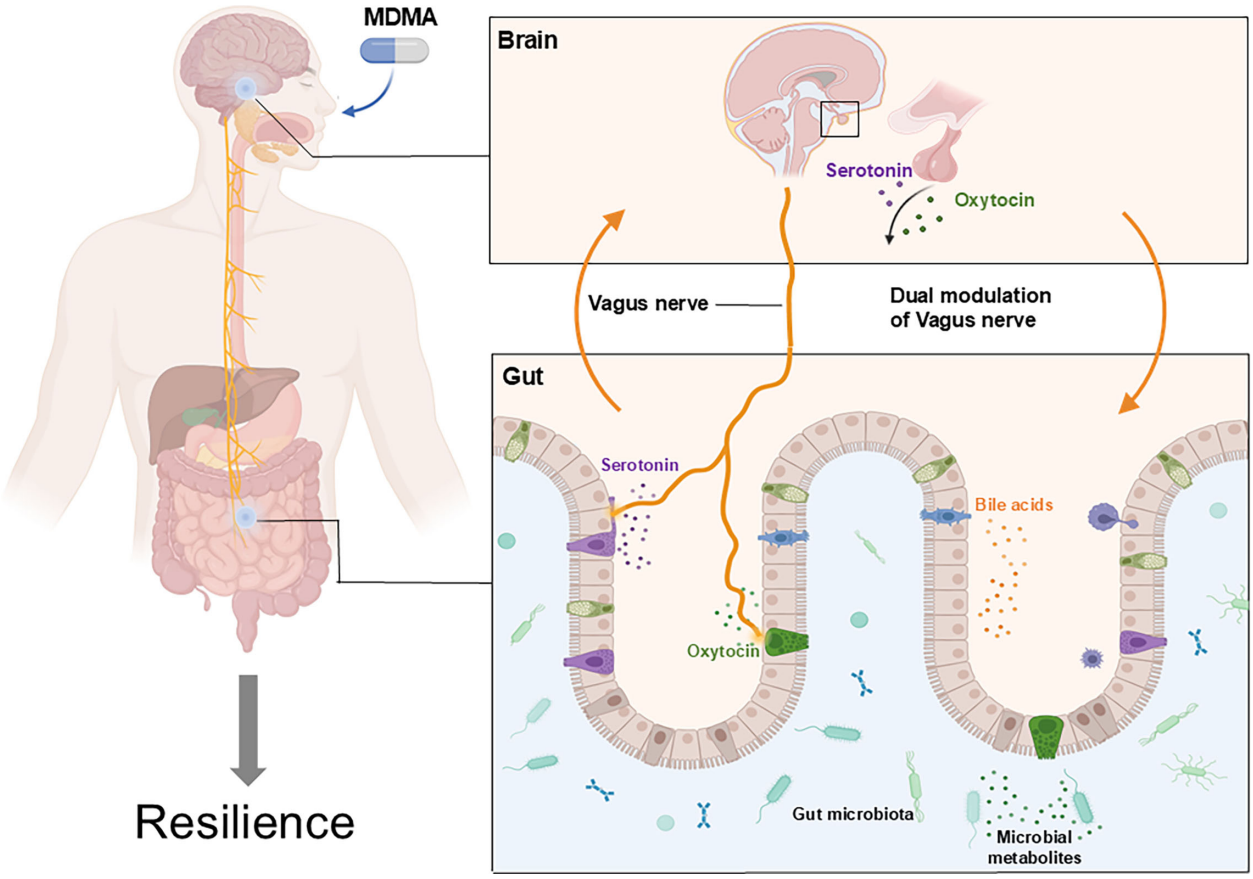


Figure 5. Vagus-dependent gut–brain signaling in MDMA-induced stress resilience. MDMA elevates central 5-HT and stimulates peripheral release of 5-HT from enterochromaffin cells, alongside oxytocin from enteroendocrine cells and the posterior pituitary. These gut-derived signals—together with bile acid changes—activate vagal afferents in the intestinal wall, relaying to brainstem nuclei. Downstream modulation of limbic and cortical circuits enhances neuroplasticity, stress resilience, and adaptive behaviors. This illustration was created using BioRender.com.

after MDMA-assisted psychotherapy. Emerging indications—including ASD, EDs, and existential distress in life-threatening illness—have shown promising initial signals of efficacy, particularly in improving social functioning and reducing anxiety. Observational studies further suggest that MDMA use may correlate with lower rates of depression and suicidality at the population level, pointing to broader resilience-enhancing properties.

Despite its therapeutic promise, MDMA carries clear risks. Acute adverse events such as hyperthermia, hyponatremia, sympathomimetic overstimulation, and potential progression to serotonin syndrome necessitate stringent monitoring and risk mitigation (e.g., fluid restriction and temperature control). Long-term neuroimaging and cognitive data indicate selective serotonergic terminal injury—amplified by hyperthermia and oxidative stress—underscoring the importance of dosing limits, controlled settings, and posttreatment follow-up to safeguard neurocognitive health.

Harmonizing dosing schedules, therapeutic modalities, and blinding approaches—such as using active low-dose comparators—will be essential to reduce bias and improve reproducibility in future trials. Incorporating biomarkers like threat-evoked fMRI, OXTR genotyping, and gut–brain axis profiles could enable patient stratification and more precise prediction of who will benefit from MDMA-assisted therapy. Well-powered, rigorous studies are required across ASD, EDs, resilience enhancement, and life-threatening illness populations, paired with mechanistic work on microbiota-mediated effects, vagal signaling, and receptor-specific actions. Longitudinal monitoring of cognition, neuroimaging changes, and adverse-event patterns will help define the long-term risk–benefit profile and guide clinical practice.

Achieving MDMA's full therapeutic promise will require close collaboration among neuroscientists, clinicians, psychotherapists, and regulators. By marrying mechanistic insights with high-quality clinical data and robust safety protocols, the field can responsibly transition MDMA-assisted treatments from research settings to approved therapies, offering new hope for patients with treatment-resistant psychiatric disorders.

Funding sources

This work received support by the Natural Science Foundation of China (to MMZ: Grant number 82501459, to JJY: Grant numbers U23A20421 and 82171189).

Acknowledgments

The authors used artificial intelligence–assisted tool (ChatGPT) to enhance the readability of this comment.

Author disclosures

The authors declare no conflict of interest related to this study.

Author contributions

MMZ, JJY, and KH conceived, drafted, and approved the final version of this work. 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 figures and tables provide accurate presentations of the original data. These corresponding authors JJY and KH take full responsibility for the submission process.

References

1. Bernschneider-Reif S, Oxler F, Freudenmann RW. The origin of MDMA ("ecstasy")–separating the facts from the myth. Pharmazie. 2006;61(11):966–72. PMID: 17152992
2. Freudenmann RW, Oxler F, Bernschneider-Reif S. The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. Addiction. 2006;101(9):1241–5. DOI: 10.1111/j.1360-0443.2006.01511.x. PMID: 16911722
3. O'Brien S, Nutt D. MDMA-assisted therapy: challenges, clinical trials, and the future of MDMA in treating behavioral disorders. CNS Spectr. 2025;30(1):e15. DOI: 10.1017/S1092852925000057. PMID: 16911722
4. Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs. 1986;18(4):319–27. DOI: 10.1080/02791072.1986.10472364. PMID: 2880946
5. Schmid Y, Bershad AK. Altered states and social bonds: effects of MDMA and serotonergic psychedelics on social behavior as a mechanism underlying substance-assisted therapy. Biol Psychiatry Cogn Neurosci Neuroimaging. 2024;9(5):490–9. DOI: 10.1016/j.bpsc.2024.02.001. PMID: 38341085; PMCID: PMC11378972
6. Shannon S, Geller J. MDMA for PTSD and beyond; a new paradigm brings hope. Front Hum Neurosci. 2024;18:1475013. DOI: 10.3389/fnhum.2024.1475013. PMID: 39723418; PMCID: PMC11669054
7. Kamilar-Britt P, Bedi G. The prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA): controlled studies in humans and laboratory animals. Neurosci Biobehav Rev. 2015;57:433–46. DOI: 10.1016/j.neubiorev.2015.08.016. PMID: 26408071; PMCID: PMC4678620
8. Bershad AK, Miller MA, Baggott MJ, de Wit H. The effects of MDMA on socio-emotional processing: does MDMA differ from other stimulants? J Psychopharmacol. 2016;30(12):1248–58. DOI: 10.1177/0269881116663120. PMID: 27562198; PMCID: PMC8753974
9. Dunlap LE, Andrews AM, Olson DE. Dark classics in chemical neuroscience: 3,4-methylenedioxymethamphetamine. ACS Chem Neurosci. 2018;9(10):2408–27. DOI: 10.1021/acschemneuro.8b00155. PMID: 30001118; PMCID: PMC6197894
10. Wolfgang AS, Fonzo GA, Gray JC, Krystal JH, Grzenda A, Widge AS, et al. MDMA and MDMA-assisted therapy. Am J Psychiatry. 2025;182(1):79–103. DOI: 10.1176/appi.ajp.20230681. PMID: 39741438
11. McKenna DJ, Peroutka SJ. Neurochemistry and neurotoxicity of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). J Neurochem. 1990;54(1):14–22. DOI: 10.1111/j.1471-4159.1990.tb13277.x. PMID: 1967141
12. Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev. 2003;55(3):463–508. DOI: 10.1124/pr.55.3.3. PMID: 12869661
13. Simantov R. Multiple molecular and neuropharmacological effects of MDMA (Ecstasy). Life Sci. 2004;74(7):803–14. DOI: 10.1016/j.lfs.2003.08.002. PMID: 14659969
14. Amato JL, Bankson MG, Yamamoto BK. Prior exposure to chronic stress and MDMA potentiates mesoaccumbens dopamine release mediated by the 5-HT1B receptor. Neuropsychopharmacology. 2007;32(4):946–54. DOI: 10.1038/sj.npp.1301174. PMID: 16885935
15. Heifets BD, Salgado JS, Taylor MD, Hoerbelt P, Cardozo Pinto DF, Steinberg EE, et al. Distinct neural mechanisms for the prosocial and rewarding properties of MDMA. Sci Transl Med. 2019;11(522):eaaw6435. DOI: 10.1126/scitranslmed.aaw6435. PMID: 31826983; PMCID: PMC7123941
16. Pomrenze MB, Vaillancourt S, Salgado JS, Raymond KB, Llorach P, Sacai H, et al. 5-HT2C receptors in the nucleus accumbens constrain the rewarding effects of MDMA. Mol Psychiatry. 2025. DOI: 10.1038/s41380-025-03128-4. PMID: 40707786
17. Walsh JJ, Llorach P, Cardozo Pinto DF, Wenderski W, Christoffel DJ, Salgado JS, et al. Systemic enhancement of serotonin signaling reverses social deficits in multiple mouse models for ASD. Neuropsychopharmacology. 2021;46(11):2000–10. DOI: 10.1038/s41386-021-01091-6. PMID: 34239048; PMCID: PMC8429585
18. Rein B, Raymond K, Boustani C, Tuy S, Zhang J, St Laurent R, et al. MDMA enhances empathy-like behaviors in mice via 5-HT release in the nucleus accumbens. Sci Adv. 2024;10(17):eadl6554. DOI: 10.1126/sciadv.adl6554. PMID: 38657057; PMCID: PMC11042730
19. Ionescu TM, Amend M, Hafiz R, Maurer A, Biswal B, Wehrl HF, et al. Mapping serotonergic dynamics using drug-modulated molecular connectivity in rats. Elife. 2025;13:RP97864. DOI: 10.7554/eLife.97864. PMID: 40372776; PMCID: PMC12080997
20. Liechti ME, Baumann C, Gamma A, Vollenweider FX. Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. Neuropsychopharmacology. 2000;22(5):513–21. DOI: 10.1016/S0893-133X(99)00148-7. PMID: 10731626
21. Liechti ME, Vollenweider FX. The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. J Psychopharmacol. 2000;14(3):269–74. DOI: 10.1177/026988110001400313. PMID: 11106307
22. Liechti ME, Vollenweider FX. Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Hum Psychopharmacol. 2001;16(8):589–98. DOI: 10.1002/hup.348. PMID: 12404538
23. Gold LH, Hubner CB, Koob GF. A role for the mesolimbic dopamine system in the psychostimulant actions of MDMA. Psychopharmacology (Berl). 1989;99(1):40–7. DOI: 10.1007/BF00634450. PMID: 2571175
24. Farrar AM, Nordstrom IH, Shelley K, Archer G, Kunstman KN, Palamar JJ, et al. MDMA: what health practitioners need to know about this common recreational drug. Dis Mon. 2025;71(3):101851. DOI: 10.1016/j.disamonth.2024.101851. PMID: 39814637; PMCID: PMC11932799
25. Hagino Y, Takamatsu Y, Yamamoto H, Iwamura T, Murphy DL, Uhl GR, et al. Effects of MDMA on extracellular dopamine and serotonin levels in mice lacking dopamine and/or serotonin transporters. Curr Neuropharmacol. 2011;9(1):91–5. DOI: 10.2174/157015911795017254. PMID: 21886569; PMCID: PMC3137209
26. Wolff K, Tsapakis EM, Pariante CM, Kerwin RW, Forsling ML, Aitchison KJ. Pharmacogenetic studies of change in cortisol on ecstasy (MDMA) consumption. J Psychopharmacol. 2012;26(3):419–28. DOI: 10.1177/0269881111415737. PMID: 21969106
27. Parrott A, Lock J, Adnum L, Thome J. MDMA can increase cortisol levels by 800% in dance clubbers. J Psychopharmacol. 2013;27(1):113–4. DOI: 10.1177/0269881112454231. PMID: 23255436
28. Forsling M, Fallon JK, Kicman AT, Hutt AJ, Cowan DA, Henry JA. Arginine vasopressin release in response to the administration of 3,4-methylenedioxymethamphetamine ("ecstasy"): is metabolism a contributory factor? J Pharm Pharmacol. 2001;53(10):1357–63. DOI: 10.1211/0022357011777855. PMID: 11697543
29. Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT. Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl). 2002;162(4):396–405. DOI: 10.1007/s00213-002-1131-1. PMID: 12172693
30. Parrott AC. Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research. Hum Psychopharmacol. 2013;28(4):289–307. DOI: 10.1002/hup.2318. PMID: 23881877
31. Dolder PC, Müller F, Schmid Y, Borgwardt SJ, Liechti ME. Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. Psychopharmacology (Berl). 2018;235(2):467–79. DOI: 10.1007/s00213-017-4650-5. PMID: 28551715; PMCID: PMC5813072
32. Baggott MJ, Garrison KJ, Coyle JR, Galloway GP, Barnes AJ, Huestis MA, et al. Effects of the psychedelic amphetamine MDA (3,4-methylenedioxy amphetamine) in healthy volunteers. J Psychoactive Drugs. 2019;51(2):108–117. DOI: 10.1080/02791072.2019.1593560. PMID: 30967099
33. Erdozain AM, Peñagarikano O. Oxytocin as treatment for social cognition, not there yet. Front Psychiatry. 2020;10:930. DOI: 10.3389/fpsyt.2019.00930. PMID: 31998152; PMCID: PMC6962227
34. Froemke RC, Young LJ. Oxytocin, neural plasticity, and social behavior. Annu Rev Neurosci. 2021;44:359–81. DOI: 10.1146/annurev-neuro-102320-102847. PMID: 33823654; PMCID: PMC8604207
35. Chaulagain RP, Shrestha Y, Shrestha H, Bhandari R, Gurung P. The neurobiological impact of oxytocin in mental health disorders: a comprehensive review. Ann Med Surg (Lond). 2025;87(3):1479–86. DOI: 10.1097/MS9.0000000000003015. PMID: 40213210; PMCID: PMC11981257
36. Matsushita H, Nishiki TI. Human social behavior and oxytocin: molecular and neuronal mechanisms. Neuroscience. 2025;570:48–54. DOI: 10.1016/j.neuroscience.2025.02.026. PMID: 39961388
37. Kirkpatrick MG, Lee R, Wardle MC, Jacob S, de Wit H. Effects of MDMA and intranasal oxytocin on social and emotional processing. Neuropsychopharmacology. 2014;39(7):1654–63. DOI: 10.1038/npp.2014.12. PMID: 24448644; PMCID: PMC4023138
38. Kirkpatrick MG, Francis SM, Lee R, de Wit H, Jacob S. Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans. Psychoneuroendocrinology. 2014;46:23–31. DOI: 10.1016/j.psyneuen.2014.04.006. PMID: 24882155; PMCID: PMC4088952
39. Kirkpatrick M, Delton AW, Robertson TE, de Wit H. Prosocial effects of MDMA: a measure of generosity. J Psychopharmacol. 2015;29(6):661–8. DOI: 10.1177/0269881115573806. PMID: 25735993
40. Parrott AC. Oxytocin, cortisol and 3,4-methylenedioxymethamphetamine: neurohormonal aspects of recreational 'ecstasy'. Behav Pharmacol 2016;27(8):649–58. DOI: 10.1097/FBP.0000000000000262. PMID: 27681116

41. Bershad AK, Weafer JJ, Kirkpatrick MG, Wardle MC, Miller MA, de Wit H. Oxytocin receptor gene variation predicts subjective responses to MDMA. Soc Neurosci. 2016;11(6):592–9. DOI: 10.1080/17470919.2016.1143026. PMID: 26787430; PMCID: PMC4988944
42. Straumann I, Avedisian I, Klaiber A, Varghese N, Eckert A, Rudin D, et al. Acute effects of R-MDMA, S-MDMA, and racemic MDMA in a randomized double-blind cross-over trial in healthy participants. Neuropsychopharmacology. 2024;50(2):362–71. DOI: 10.1038/s41386-024-01972-6. PMID: 39179638; PMCID: PMC11631982
43. Atila C, Nikaj A, Leibnitz S, Liechti ME, Christ-Crain M. Neurophysin I: a reliable, novel, and robust biomarker for oxytocin. Eur J Endocrinol. 2025;192(4):502–10. DOI: 10.1093/ejendo/lvaf078. PMID: 40209095
44. Atila C, Camerin SJ, Liechti ME, Christ-Crain M. The effect of MDMA on anterior pituitary hormones: a secondary analysis of a randomized placebo-controlled trial. Endocr Connect. 2025;14(6):e250254. DOI: 10.1530/EC-25-0254. PMID: 40459963; PMCID: PMC12177877
45. Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT1A receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy"). Neuroscience. 2007;146(2):509–14. DOI: 10.1016/j.neuroscience.2007.02.032. PMID: 17383105
46. Hunt GE, McGregor IS, Cornish JL, Callaghan PD. MDMA-induced c-fos expression in oxytocin-containing neurons is blocked by pretreatment with the 5-HT-1A receptor antagonist WAY 100635. Brain Res Bull. 2011;86(1-2):65–73. DOI: 10.1016/j.brainresbull.2011.06.011. PMID: 21745546
47. Broadbear JH, Tunstall B, Beringer K. Examining the role of oxytocin in the interoceptive effects of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') using a drug discrimination paradigm in the rat. Addict Biol. 2011;16(2):202–14. DOI: 10.1111/j.1369-1600.2010.00267.x. PMID: 21070509
48. Avgana H, Toledano RS, Akirav I. Examining the role of oxytocinergic signaling and neuroinflammatory markers in the therapeutic effects of MDMA in a rat model for PTSD. Pharmaceuticals (Basel). 2024;17(7):846. DOI: 10.3390/ph17070846. PMID: 39065697; PMCID: PMC11279644
49. Chang L, Wei Y, Hashimoto K. Brain-gut-microbiota axis in depression: a historical overview and future directions. Brain Res Bull. 2022;182:44–56. DOI: 10.1016/j.brainresbull.2022.02.004. PMID: 35151796
50. Wei Y, Wang T, Liao L, Fan X, Chang L, Hashimoto K. Brain-spleen axis in health and diseases: a review and future perspective. Brain Res Bull. 2022;182:130–140. DOI: 10.1016/j.brainresbull.2022.02.008. PMID: 35157987
51. Hashimoto K. Neuroinflammation through the vagus nerve-dependent gut-microbiota-brain axis in treatment-resistant depression. Prog Brain Res. 2023;278:61–77. DOI: 10.1016/bs.pbr.2023.01.003. PMID: 37414494
52. Ma L, Wang HB, Hashimoto K. The vagus nerve: an old but new player in brain-body communication. Brain Behav Immun. 2025;124:28–39. DOI: 10.1016/j.bbi.2024.11.023. PMID: 39566667
53. Yue Y, Wan X, Liu G, Zhu T, Xu D, Zhao M, et al. Subdiaphragmatic vagotomy reduces hypothalamic oxytocin expression and blood levels after oral MDMA administration in male rats. Prog Neuropsychopharmacol Biol Psychiatry. 2025;137:111260. DOI: 10.1016/j.pnpbp.2025.111260. PMID: 39855536
54. Collins SA, Gudelsky GA, Yamamoto BK. MDMA-induced loss of parvalbumin interneurons within the dentate gyrus is mediated by 5-HT2A and NMDA receptors. Eur J Pharmacol. 2015;761:95–100. DOI: 10.1016/j.ejphar.2015.04.035. PMID: 25936514; PMCID: PMC4532576
55. García-Pardo MP, Miñarro J, Llansola M, Felipo V, Aguilar MA. Role of NMDA and AMPA glutamatergic receptors in the effects of social defeat on the rewarding properties of MDMA in mice. Eur J Neurosci. 2019;50(3):2623–34. DOI: 10.1111/ejn.14190. PMID: 30276890
56. Liechti ME. Effects of MDMA on body temperature in humans. Temperature (Austin). 2014;1(3):192–200. DOI: 10.4161/23328940.2014.955433. PMID: 27626046; PMCID: PMC5008716
57. Faria AC, Carmo H, Carvalho F, Silva JP, Bastos ML, Dias da Silva D. Drinking to death: hyponatraemia induced by synthetic phenethylamines. Drug Alcohol Depend. 2020;212:108045. DOI: 10.1016/j.drugalcdep.2020.108045. PMID: 32460203
58. van Amsterdam J, Brunt TM, Pierce M, van den Brink W. Hard boiled: alcohol use as a risk factor for MDMA-induced hyperthermia: a systematic review. Neurotox Res. 2021;39(6):2120–33. DOI: 10.1007/s12640-021-00416-z. PMID: 34554408; PMCID: PMC8639540
59. Baldo BA. The entactogen 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) as a treatment aid in psychotherapy and its safety concerns. Arch Toxicol. 2024;98(8):2409–27. DOI: 10.1007/s00204-024-03765-8. PMID: 38743292
60. Demirkiran M, Jankovic J, Dean JM. Ecstasy intoxication: an overlap between serotonin syndrome and neuroleptic malignant syndrome. Clin Neuropharmacol. 1996;19(2):157–64. DOI: 10.1097/00002826-199619020-00004. PMID: 8777769
61. Dumont GJ, Verkes RJ. A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. J Psychopharmacol. 2006;20(2):176–87. DOI: 10.1177/0269881106063271. PMID: 16510476
62. Atila C, Straumann I, Vizeli P, Beck J, Monnerat S, Holze F, et al. Oxytocin and the role of fluid restriction in MDMA-induced hyponatremia: A secondary analysis of 4 randomized clinical trials. JAMA Netw Open. 2024;7(11):e2445278. DOI: 10.1001/jamanetworkopen.2024.45278. PMID: 39546312; PMCID: PMC11568463
63. Rana S, Canfield JR, Ward CS, Sprague JE. Bile acids and the gut microbiome are involved in the hyperthermia mediated by 3,4-methylenedioxymethamphetamine (MDMA). Sci Rep. 2024;14(1):14485. DOI: 10.1038/s41598-024-65433-2. PMID: 38914648; PMCID: PMC11196659
64. Colcott J, Guerin AA, Carter O, Meikle S, Bedi G. Side-effects of MDMA-assisted psychotherapy: a systematic review and meta-analysis. Neuropsychopharmacology. 2024;49(8):1208–26. DOI: 10.1038/s41386-024-01865-8. PMID: 38654146; PMCID: PMC11224236
65. Urban NB, Girgis RR, Talbot PS, Kegeles LS, Xu X, Frankle WG, et al. Sustained recreational use of ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: a PET study with [^{11}C]DASB and [^{11}C]MDL 100907. Neuropsychopharmacology. 2012;37(6):1465–73. DOI: 10.1038/npp.2011.332. PMID: 22353758; PMCID: PMC3327851
66. Roberts CA, Jones A, Montgomery C. Meta-analysis of molecular imaging of serotonin transporters in ecstasy/polydrug users. Neurosci Biobehav Rev. 2016;63:158–67. DOI: 10.1016/j.neubiorev.2016.02.003. PMID: 26855234
67. Müller F, Brändle R, Liechti ME, Borgwardt S. Neuroimaging of chronic MDMA ("ecstasy") effects: A meta-analysis. Neurosci Biobehav Rev. 2019;96:10–20. DOI: 10.1016/j.neubiorev.2018.11.004. PMID: 30439373
68. Montgomery C, Roberts CA. Neurological and cognitive alterations induced by MDMA in humans. Exp Neurol. 2022;347:113888. DOI: 10.1016/j.expneurol.2021.113888. PMID: 34624331
69. Reneman L, Majoie CB, Habraken JB, den Heeten GJ. Effects of ecstasy (MDMA) on the brain in abstinent users: initial observations with diffusion and perfusion MR imaging. Radiology. 2001;220(3):611–7. DOI: 10.1148/radiol.2202001602. PMID: 11526257
70. Cowan RL, Lyoo IK, Sung SM, Ahn KH, Kim MJ, Hwang J, et al. Reduced cortical gray matter density in human MDMA (Ecstasy) users: a voxel-based morphometry study. Drug Alcohol Depend. 2003;72(3):225–35. DOI: 10.1016/j.drugalcdep.2003.07.001. PMID: 14643939
71. Thomasius R, Zapletalova P, Petersen K, Buchert R, Andresen B, Wartberg L, et al. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. J Psychopharmacol. 2006;20(2):211–25. DOI: 10.1177/0269881106059486. PMID: 16510479
72. Hashimoto K, Goromaru T. Reduction of [3H]6-nitroquipazine-labelled 5-hydroxytryptamine uptake sites in rat brain by 3,4-methylenedioxymethamphetamine. Fundam Clin Pharmacol. 1990;4(6):635–41. DOI: 10.1111/j.1472-8206.1990.tb00043.x. PMID: 1710592
73. Hashimoto K, Goromaru T. Reduction of in vivo binding of [3H]paroxetine in mouse brain by 3,4-methylenedioxymethamphetamine. Neuropharmacology. 1990;29(7):633–9. DOI: 10.1016/0028-3908(90)90024-l. PMID: 1696701
74. Hashimoto K, Maeda H, Goromaru T. Effects of benzylpiperazine derivatives on the neurotoxicity of 3,4-methylenedioxymethamphetamine in rat brain. Brain Res. 1992;590(1-2):341–4. DOI: 10.1016/0006-8993(92)91119-y. PMID: 1384935
75. Zhang L, Shirayama Y, Shimizu E, Iyo M, Hashimoto K. Protective effects of minocycline on 3,4-methylenedioxymethamphetamine-induced neurotoxicity in serotonergic and dopaminergic neurons of mouse brain. Eur J Pharmacol. 2006;544(1-3):1–9. DOI: 10.1016/j.ejphar.2006.05.047. PMID: 16859675
76. Bonkale WL, Austin MC. 3,4-Methylenedioxymethamphetamine induces differential regulation of tryptophan hydroxylase 2 protein and mRNA levels in the rat dorsal raphe nucleus. Neuroscience. 2008;155(1):270–6. DOI: 10.1016/j.neuroscience.2008.03.086. PMID: 18515011; PMCID: PMC2505057
77. O'Hearn E, Battaglia G, De Souza EB, Kuhar MJ, Molliver ME. Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: immunocytochemical evidence for neurotoxicity. J Neurosci. 1988;8(8):2788–803. DOI: 10.1523/JNEUROSCI.08-08-02788.1988. PMID: 2457659; PMCID: PMC6569396
78. Costa G, Gołembiowska K. Neurotoxicity of MDMA: main effects and mechanisms. Exp Neurol. 2022;347:113894. DOI: 10.1016/j.expneurol.2021.113894. PMID: 34655576
79. McCann UD, Slate SO, Ricaurte GA. Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy'). Drug Saf. 1996;15(2):107–15. DOI: 10.2165/00002018-199615020-00003. PMID: 8884162

80. Ricaurte GA, Forno LS, Wilson MA, DeLanney LE, Irwin I, Molliver ME, et al. (±)3,4-Methylenedioxymethamphetamine selectively damages central serotonergic neurons in nonhuman primates. JAMA. 1988;260(1):51–5. PMID: 2454332
81. Ricaurte GA, DeLanney LE, Wiener SG, Irwin I, Langston JW. 5-Hydroxyindoleacetic acid in cerebrospinal fluid reflects serotonergic damage induced by 3,4-methylenedioxymethamphetamine in CNS of non-human primates. Brain Res. 1988;474(2):359–63. DOI: 10.1016/0006-8993(88)90451-9. PMID: 2463059
82. Ricaurte GA, Martello AL, Katz JL, Martello MB. Lasting effects of (+−)-3,4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates: neurochemical observations. J Pharmacol Exp Ther. 1992;261(2):616–22. PMID: 1374470
83. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of {±}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. J Psychopharmacol. 2011;25(4):439–52. DOI: 10.1177/0269881110378371. PMID: 20643699; PMCID: PMC3122379
84. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. J Psychopharmacol. 2013;27(1):28–39. DOI: 10.1177/0269881112456611. PMID: 23172889; PMCID: PMC3573678
85. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. Lancet Psychiatry. 2018;5(6):486–97. DOI: 10.1016/S2215-0366(18)30135-4. PMID: 29728331
86. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27(6):1025–33. DOI: 10.1038/s41591-021-01336-3. PMID: 33972795 PMCID: PMC8205851
87. Mitchell JM, Ot'alora GM, van der Kolk B, Shannon S, Bogenschutz M, Gelfand Y, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. Nat Med. 2023;29(10):2473–80. DOI: 10.1038/s41591-023-02565-4. PMID: 37709999; PMCID: PMC10579091
88. Reardon S. MDMA therapy for PTSD rejected by FDA panel. Nature. 2024. DOI: 10.1038/d41586-024-01622-3. PMID: 38844808
89. Kupferschmidt K. What's next for psychedelics after MDMA rejection? Science. 2024;385(6710):702–703. DOI: 10.1126/science.ads4470. PMID: 39146407
90. Nogrady B. Australia's approval of MDMA and psilocybin for PTSD and depression is premature, say critics. BMJ. 2023;382:1599. DOI: 10.1136/bmj.p1599. PMID: 37433614
91. Haridy R. Australia to prescribe MDMA and psilocybin for PTSD and depression in world first. Nature. 2023;619(7969):227–8. DOI: 10.1038/d41586-023-02093-8. PMID: 37386185
92. Nutt DJ, Hunt P, Schlag AK, Fitzgerald P. The Australia story: current status and future challenges for the clinical applications of psychedelics. Br J Pharmacol. 2024. DOI: 10.1111/bph.17398. PMID: 39701143
93. Jing Yong AS, Bratuskins S, Sultani MS, Blakeley B, Davey CG, Bell JS. Safety and efficacy of methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in post-traumatic stress disorder: an overview of systematic reviews and meta-analyses. Aust N Z J Psychiatry. 2025;59(4):339–360. DOI: 10.1177/00048674251315642. PMID: 39979849; PMCID: PMC11924292
94. Wilkinson ST, Sanacora G. Issues in clinical trial design-lessons from the FDA's rejection of MDMA. JAMA Psychiatry. 2025;82(6):545–6. DOI: 10.1001/jamapsychiatry.2025.0442. PMID: 40238126
95. Zhang X, Hack LM, Bertrand C, Hilton R, Gray NJ, Boyar L, et al. Negative affect circuit subtypes and neural, behavioral, and affective responses to MDMA: A randomized clinical trial. JAMA Netw Open. 2025;8(4):e257803. DOI: 10.1001/jamanetworkopen.2025.7803. PMID: 40305021; PMCID: PMC12044494
96. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018;392(10146):508–20. DOI: 10.1016/S0140-6736(18)31129-2. PMID: 30078460; PMCID: PMC7398158
97. Danforth AL, Struble CM, Yazar-Klosinski B, Grob CS. MDMA-assisted therapy: a new treatment model for social anxiety in autistic adults. Prog Neuropsychopharmacol Biol Psychiatry. 2016;64:237–49. DOI: 10.1016/j.pnpbp.2015.03.011. PMID: 25818246
98. Mithoefer MC, Grob CS, Brewerton TD. Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. Lancet Psychiatry. 2016;3(5):481–8. DOI: 10.1016/S2215-0366(15)00576-3. PMID: 27067625
99. Chaliha D, Mamo JC, Albrecht M, Lam V, Takechi R, Vaccarezza M. A systematic review of the MDMA model to address social impairment in autism. Curr Neuropharmacol. 2021;19(7):1101–54. DOI: 10.2174/1570159×19666210101130258. PMID: 33388021; PMCID: PMC8686313
100. Kaur H, Karabulut S, Gauld JW, Fagot SA, Holloway KN, Shaw HE, et al. Balancing therapeutic efficacy and safety of MDMA and novel MDXX analogues as novel treatments for autism spectrum disorder. Psychedelic Med (New Rochelle). 2023;1(3):166–85. DOI: 10.1089/psymed.2023.0023. PMID: 40046567; PMCID: PMC11661495
101. Danforth AL, Grob CS, Struble C, Feduccia AA, Walker N, Jerome L, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. Psychopharmacology (Berl). 2018;235(11):3137–48. DOI: 10.1007/s00213-018-5010-9. PMID: 30196397; PMCID: PMC6208958
102. Treasure J, Duarte TA, Schmidt U. Eating disorders. Lancet. 2020;395(10227):899–911. DOI: 10.1016/S0140-6736(20)30059-3. PMID: 32171414
103. Calder A, Mock S, Friedli N, Pasi P, Hasler G. Psychedelics in the treatment of eating disorders: rationale and potential mechanisms. Eur Neuropsychopharmacol. 2023;75:1–14. DOI: 10.1016/j.euroneuro.2023.05.008. PMID: 37352816
104. Brewerton TD, Lafrance A, Mithoefer MC. The potential use of N-methyl-3,4-methylenedioxyamphetamine (MDMA) assisted psychotherapy in the treatment of eating disorders comorbid with PTSD. Med Hypotheses. 2021;146:110367. DOI: 10.1016/j.mehy.2020.110367. PMID: 33203569
105. Brewerton TD, Wang JB, Lafrance A, Pamplin C, Mithoefer M, Yazar-Klosinki B, et al. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. J Psychiatr Res. 2022;149:128–35. DOI: 10.1016/j.jpsychires.2022.03.008. PMID: 35272210
106. McCorkle R, Quint-Benoliel J. Symptom distress, current concerns and mood disturbance after diagnosis of life-threatening disease. Soc Sci Med. 1983;17(7):431–8. DOI: 10.1016/0277-9536(83)90348-9. PMID: 6867788
107. Reiche S, Hermle L, Gutwinski S, Jungaberle H, Gasser P, Majić T. Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2018;81:1–10. DOI: 10.1016/j.pnpbp.2017.09.012. PMID: 28947181
108. Schimmers N, Breeksema JJ, Smith-Apeldoorn SY, Veraart J, van den Brink W, Schoevers RA. Psychedelics for the treatment of depression, anxiety, and existential distress in patients with a terminal illness: a systematic review. Psychopharmacology (Berl). 2022;239(1):15–33. DOI: 10.1007/s00213-021-06027-y. PMID: 34812901
109. Sicignano D, Snow-Caroti K, Hernandez AV, White CM. The impact of psychedelic drugs on anxiety and depression in advanced cancer or other life-threatening disease: a systematic review with meta-analysis. Am J Clin Oncol. 2023;46(6):236–45. DOI: 10.1097/COC.0000000000000998. PMID: 36907889
110. Schipper S, Nigam K, Schmid Y, Piechotta V, Ljuslin M, Beaussant Y, et al. Psychedelic-assisted therapy for treating anxiety, depression, and existential distress in people with life-threatening diseases. Cochrane Database Syst Rev. 2024;9(9):CD015383. DOI: 10.1002/14651858.CD015383.pub2. PMID: 39260823; PMCID: PMC11390284
111. Wolfson PE, Andries J, Feduccia AA, Jerome L, Wang JB, Williams E, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. Sci Rep. 2020;10(1):20442. DOI: 10.1038/s41598-020-75706-1. PMID: 33235285; PMCID: PMC7686344
112. Jones GM, Nock MK. MDMA/ecstasy use and psilocybin use are associated with lowered odds of psychological distress and suicidal thoughts in a sample of US adults. J Psychopharmacol. 2022;36(1):46–56. DOI: 10.1177/02698811211058923. PMID: 34983249
113. Jones GM, Nock MK. Lifetime use of MDMA/ecstasy and psilocybin is associated with reduced odds of major depressive episodes. J Psychopharmacol. 2022;36(1):57–65. DOI: 10.1177/02698811211066714. PMID: 34983261
114. Yang KH, Han BH, Palamar JJ. Past-year hallucinogen use in relation to psychological distress, depression, and suicidality among US adults. Addict Behav. 2022;132:107343. DOI: 10.1016/j.addbeh.2022.107343. PMID: 35525189; PMCID: PMC9177770
115. Netzer O, Nagal N, Stern Y, Polinsky T, Gross R, Admon R, et al. Trauma under psychedelics: how psychoactive substances impact trauma processing. World Psychiatry. 2025;24(3):444–5. DOI: 10.1002/wps.21363. PMID: 40948086; PMCID: PMC12434345
116. Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes. 2013;20(1):14–21. DOI: 10.1097/MED.0b013e32835bc703. PMID: 23222853; PMCID: PMC3708472

117. Mawe GM, Hoffman JM. Serotonin signalling in the gut–functions, dysfunctions and therapeutic targets. Nat Rev Gastroenterol Hepatol. 2013;10(8):473–86. DOI: 10.1038/nrgastro.2013.105. PMID: 23797870; PMCID: PMC4048923
118. Guzel T, Mirowska-Guzel D. The role of serotonin neurotransmission in gastrointestinal tract and pharmacotherapy. Molecules. 2022;27(5):1680. DOI: 10.3390/molecules27051680. PMID: 35268781; PMCID: PMC8911970
119. Qu Y, Eguchi A, Wan X, Ma L, Chang L, Shan J, et al. Repeated use of 3,4-methylenedioxymethamphetamine is associated with the resilience in mice after chronic social defeat stress: a role of gut-microbiota-brain axis. Psychiatry Res. 2023;320:115020. DOI: 10.1016/j.psychres.2022.115020. PMID: 36571897
120. Qu Y, Eguchi A, Ma L, Wan X, Mori C, Hashimoto K. Role of the gut-brain axis via the subdiaphragmatic vagus nerve in stress resilience of 3,4-methylenedioxymethamphetamine in mice exposed to chronic restraint stress. Neurobiol Dis. 2023;189:106348. DOI: 10.1016/j.nbd.2023.106348. PMID: 37956855
121. Zhao M, Eguchi A, Murayama R, Xu D, Zhu T, Xu B, et al. Repeated intermittent administration of 3,4-methylenedioxymethamphetamine mitigates demyelination in the brain from cuprizone-treated mice. Eur J Pharmacol. 2025;991:177345. DOI: 10.1016/j.ejphar.2025.177345. PMID: 39904416
122. Wan X, Eguchi A, Murayama R, Mori C, Hashimoto K. Intermittent MDMA attenuates ovariectomy-induced bone mineral density via a gut microbiota-bone axis. Clin Pharmacol Neurosci. DOI: 10.9758/cpn.25.1309.
123. Xu D, Eguchi A, Murayama R, Liu G, Zhao M, Zhu T, et al. Effects of 3,4-methylenedioxymethamphetamine on the gut microbiota and metabolites in the small intestine, cecum, and colon of male rats. Prog Neuropsychopharmacol Biol Psychiatry. 2025;136:111223. DOI: 10.1016/j.pnpbp.2024.111223. PMID: 39701173
124. Danhof HA, Lee J, Thapa A, Britton RA, Di Rienzi SC. Microbial stimulation of oxytocin release from the intestinal epithelium via secretin signaling. Gut Microbes. 2023;15(2):2256043. DOI: 10.1080/19490976.2023.2256043. PMID: 37698879; PMCID: PMC10498800
125. Steele TD, McCann UD, Ricaurte GA. 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"): pharmacology and toxicology in animals and humans. Addiction. 1994;89(5):539–51. DOI: 10.1111/j.1360-0443.1994.tb03330.x. PMID: 7913850
126. Green AR, Cross AJ, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"). Psychopharmacology (Berl). 1995;119(3):247–60. DOI: 10.1007/BF02246288. PMID: 7675958

Genomic Press
Psychedelics
The Journal of Psychedelic and Psychoactive Drug Research

Psychedelics

OPEN

RESEARCH REPORT

Single-dose psychedelic enhances cognitive flexibility and reversal learning in mice weeks after administration

Elizabeth J. Brouns[1], Tyler G. Ekins[1,2], and Omar J. Ahmed[1,2,3,4,5]

[1]Department of Psychology, University of Michigan, Ann Arbor, MI 48109
[2]Michigan Psychedelic Center, University of Michigan, Ann Arbor, MI 48109
[3]Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI 48109
[4]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109
[5]Center of Computational Medicine & Bioinformatics University of Michigan, Ann Arbor, MI 48109

Corresponding Author: Omar J. Ahmed, Department of Psychology, University of Michigan, 530 Church St., Ann Arbor, MI 48109.
E-mail: ojahmed@umich.edu

Psychedelics May 2025;1(3):29–35;
doi: https://doi.org/10.61373/pp025r.0002

Psychedelic compounds have demonstrated remarkable therapeutic potential for treating neuropsychiatric disorders by promoting sustained neuroplasticity in the prefrontal cortex (PFC). Cognitive flexibility—the ability to adapt previously learned rules to novel situations—represents a critical PFC function that is frequently impaired in depression, PTSD, and neurodegenerative conditions. In this study, we demonstrate that a single administration of the selective serotonin 2A receptor agonist 25CN-NBOH produces significant, long-lasting improvements in cognitive flexibility in both male and female mice when measured 2–3 weeks posttreatment. Using a novel automated sequential learning paradigm, psychedelic-treated mice showed superior adaptability in rule reversal tasks compared to saline controls, as evidenced by enhanced poke efficiency, higher percentages of correct trials, and increased reward acquisition. These behavioral findings complement existing cellular research showing psychedelic-induced structural remodeling in the PFC and uniquely demonstrate sustained cognitive benefits persisting weeks after a single psychedelic dose. Our automated behavioral task provides a high-throughput method for evaluating cognitive flexibility effects of various psychedelic compounds, offering important implications for therapeutic applications in conditions characterized by cognitive rigidity, including depression, PTSD, and potentially Alzheimer's disease.

Keywords: Cognitive flexibility, neuroplasticity, psychedelic therapy, reversal learning, serotonin 2a receptor.

Introduction

Psychedelic drugs have been used to treat multiple neuropsychiatric disorders, including major depressive disorder, posttraumatic stress disorder (PTSD), and substance use disorders (1–14). These neuropsychiatric disorders are precipitated by chronic stress, which leads to both structural and functional changes in the prefrontal cortex (PFC) in humans and rodents (15–22). The therapeutic potential of psychedelics may be due to their ability to restore neural circuits damaged in these pathologies by boosting synaptic activity (23–31).

The PFC contributes to the control of many cognitive functions, including working memory, memory retrieval, decision-making, and executive function (32, 33). One key aspect of executive function is the ability to apply previously learned rules to novel situations, also known as cognitive flexibility (33, 34). Flexibility disruptions are associated with neuropsychiatric disorders, such as depression and PTSD, as well as neurodevelopmental and neurodegenerative disorders (34, 35). Cognitive flexibility has been examined using tasks such as the Flanker Task, Stroop Task, and the Wisconsin Card Sorting Task; however, these kinds of tasks are largely limited to humans (36). In contrast, most cognitive flexibility tasks for rodents can be classified as either attentional set-shifting paradigms, which involve the learning of two separate rules and associated cues, or reversal learning, which involves applying a learned rule to a reversed scenario (37, 38). Reversal learning is an effective method for studying cognitive flexibility in rodents, including mice (38–40). Reversal learning paradigms can be extremely diverse, varying in the kind of tasks being taught to the number and timing of reversals involved in the paradigm. These details are critical when evaluating the existing literature's examination of cognitive flexibility through reversal learning.

25CN-NBOH is a psychedelic agent with high affinity and selectivity for the serotonin 2A (5-HT_{2A}) receptor (41–43). It has demonstrated psychedelic-like effects and is commonly used in the study of psychedelic mechanisms in rodents (44–46). 25CN-NBOH has much stronger affinity for 5-HT_{2A} receptors (50–100x higher affinity) in comparison to the closely related 5-HT_{2B} and 5-HT_{2C} receptors. Compared to 25CN-NBOH, other psychedelic drugs have a lower ratio of 5-HT_{2A} to 5-HT_{2B} or 5-HT_{2C} affinity (47–49). As 5-HT_{2A} receptor activation, specifically, has previously been shown to be required for psychedelic-induced synaptogenesis that might contribute to behavioral changes, this high affinity and high selectivity 5-HT_{2A} receptor agonist was chosen as the psychedelic drug for the present study of psychedelic effects on cognitive flexibility.

As single psychedelic administrations promote structural changes in the PFC that last for several weeks (24, 29, 31), here we asked whether a single psychedelic administration could also induce a weeks-long enhancement of flexible learning ability in mice. We conducted a reversal learning task in which female and male mice were administered a single dose of a psychedelic drug or saline and found enhanced performance on the reversal task which persists for at least 3 weeks after one psychedelic dose

Results

To determine whether psychedelic treatment induces long-lasting changes in flexible learning ability, we treated female and male mice with a single dose of the selective serotonin 2A (5-HT_{2A}) receptor agonist 25CN-NBOH (41–45) or saline via intraperitoneal injection. Following a waiting period of one day, light food restriction for 2 days, and 5 days of training with the Feeding Experimentation Device version 3 (FED3) device, we utilized a forward sequence learning protocol (Figure 1A). Mice learned to initiate a trial with a left poke and then had to poke right within the subsequent 30 s to receive a food pellet (Figure 1B). Following 6 days of 4 h/day forward protocol sessions, the required sequential poking pattern was reversed. For another 6 days of 4-h sessions, mice were then required to poke right and then poke left within 30 s to receive the food pellet (Figure 1C). This reversal of the experimental protocol is indicative of flexible learning: we measured the degree to which a mouse is able to adapt the previously learned 1 poke/hole sequence rule to a novel situation, which, in this case, was the reversed direction.

We found that psychedelic and saline-treated mice learned the forward task at similar rates, as reflected by the poke efficiency, which represents the proportion of pellets dispensed out of all pokes (Figure 2A), and the percentage of correct trials initiated out of all trials initiated (Figure 2B). While the change in forward learning poke efficiency and percentage correct was not affected by psychedelic treatment (poke efficiency: saline $R^2 = 0.25$, NBOH $R^2 = 0.20$; $F_{(1,557)} = .1721$, $P = 0.6784$; percent correct: saline $R^2 = 0.16$, NBOH $R^2 = 0.13$; $F_{(1,431)} = .7771$, $P = 0.3785$), the

Received: 18 November 2024. Revised: 15 December 2024 and 30 March 2025. Accepted: 2 April 2025.
Published online: 22 April 2025.

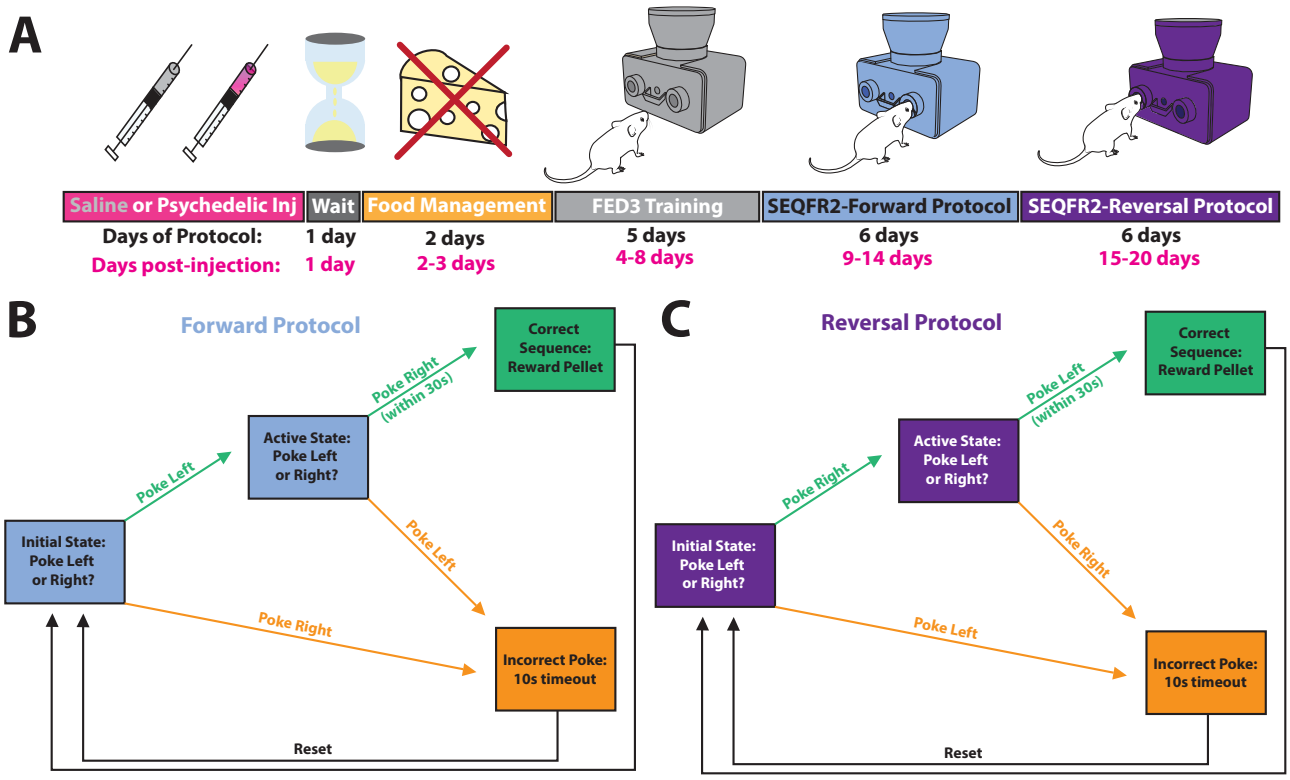


Figure 1. Experimental timeline and overview. (A) Experimental timeline (65). (B) Schematic of the SEQFR2-forward protocol. Mice have to sequentially poke left and then right within 30 s to earn a reward pellet. (C) Schematic of the SEQFR2-reversal protocol. Mice now are required to poke right and then left within 30 s to get a reward pellet.

NBOH-treated group accumulated more reward pellets than the saline group (Figure 2C; saline: $R^2 = 0.18$, NBOH: $R^2 = 0.27$; $F_{(1,620)} = 7.513$, $P = 0.0063$), indicating an increased initiation of trials per hour with the FED3 (Figure 2C), as the baseline and learning rates were similar between groups (Supplemental Figure 1).

Importantly, during the reversal phase, measured 15–20 days after the single injection, psychedelic treatment resulted in significantly increased learning ability. This is indicated by the increased the efficiency of nose pokes (Supplemental Figure 2; Figure 2D; saline: $R^2 = 0.11$, NBOH: $R^2 = 0.32$; $F_{(1,528)} = 21.91$, $P < 0.0001$), the percent correct trials initiated (Figure 2E; saline: $R^2 = 0.11$, NBOH: $R^2 = 0.23$; $F_{(1,401)} = 6.629$, $P = 0.0104$), and again by the higher total number of pellets obtained (Figure 2F; saline: $R^2 = 0.10$, NBOH: $R^2 = 0.37$; $F_{(1,620)} = 20.74$, $P < 0.0001$).

We confirmed the robustness of these findings by conducting Welch's one-sided t-tests after calculating individual linear regression curves for each animal, and found that NBOH-treated mice (poke efficiency: $M = 0.036$, $SD = 0.026$; percent correct: $M = 0.084$, $SD = 0.052$), relative to saline treated mice (poke efficiency: $M = 0.016$, $SD = 0.015$; percent correct: $M = 0.043$, $SD = 0.049$) perform better on average in the reversal phase (reversal poke efficiency: $t(17.40) = 2.29$, $p = 0.017$, Cohen's $d = 0.928$; reversal percent correct: $t(22.92) = 2.07$, $p = 0.0252$, Cohen's $d = 0.814$). This was consistent with the aforementioned results. Also consistent with the above findings, the individual linear regression analysis showed that there were no significant differences in both the forward poke efficiency ($t(22.58) = 0.380$, $p = 0.354$, Cohen's $d = 0.152$) and forward percent correct ($t(23.78) = -0.729$, $p = 0.763$, Cohen's $d = -0.286$) metrics between NBOH (forward poke efficiency: $M = 0.035$, $SD = 0.026$; percent correct: $M = 0.049$, $SD = 0.050$) and saline-treated mice (forward poke efficiency: $M = 0.031$, $SD = 0.026$; percent correct: $M = 0.063$, $SD = 0.053$).

Finally, we considered sex as a biological variable to determine whether NBOH improved learning in both sexes. We found that, consistent with our sex-independent results (Figure 2), NBOH treatment did not affect poke efficiency during the forward phase (Female: $F_{(1,334)} = 0.986$, $P = .322$; Male: $F_{(1,219)} = 0.004$, $P = 0.952$), but significantly enhanced poke efficiency during the reversal phase (Figure 3; Female; $F_{(1,319)} = 16$, $P < .0001$; Male: $F_{(1,205)} = 8.3$, $P = 0.0044$). Thus, psychedelic treatment induced a weeks-long lasting enhancement of reversal learning in both male and female mice. When comparing male and female poke efficiency, we found that male mice treated with saline performed slightly better than female mice in both the forward and reversal phases ($P = .0011$; $P = 0.0218$), and male mice treated with NBOH performed better in the reversal phase than female mice ($P = 0.0206$).

Discussion

This study sought to examine the effects of a single psychedelic dose on flexible learning. We found that even 2–3 weeks after a single dose, NBOH significantly enhanced reversal learning ability. Poke efficiency, percentage of correct trials, and cumulative pellets dispensed were all improved during the reversal phase in mice that received NBOH compared to mice that received saline. Both male and female mice displayed improved learning during the reversal phase with psychedelic treatment, highlighting the therapeutic potential of psychedelic medicine to boost cognitive flexibility in both sexes. The estrous cycle can influence cognitive flexibility performance in rodents (50). The task design utilized in our study (6 days for each of the forward and reversal phases) encompasses more than the full length of a mouse estrous cycle (4–5 days) and the analysis metric utilized here examines changes in the slope of learning across the full 6 days, thus calculating learning rates over the course of at least one full estrous cycle. Future work will help to better understand the precise influence of estrous cycle on higher temporal resolution changes in reversal learning properties.

This study contrasts with previous preclinical psychedelic reversal learning studies in terms of drug administration timepoints (46, 51–54). We administered the psychedelic or saline control 15 days before the

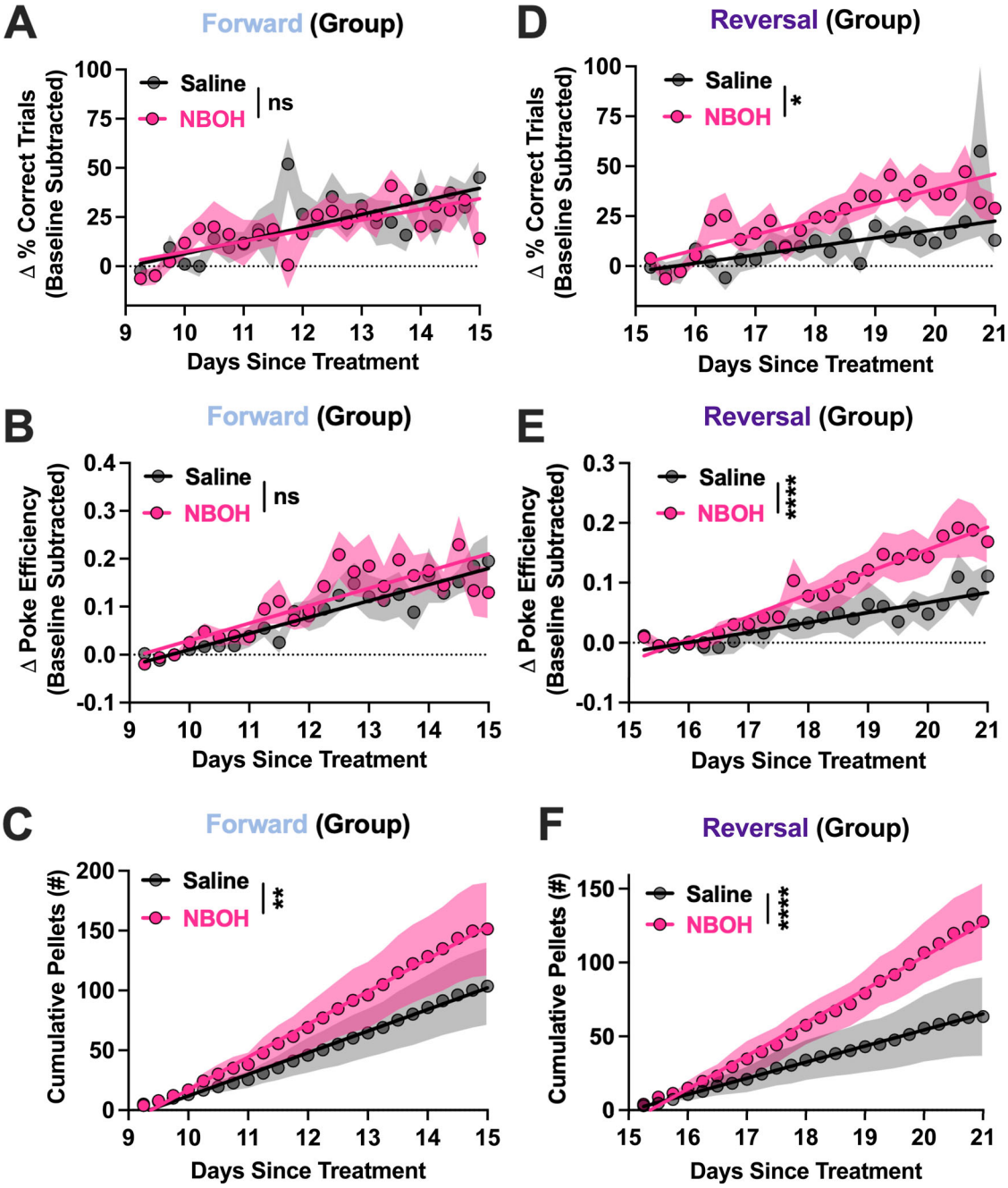


Figure 2. Single-dose psychedelic treatment induces a lasting reversal learning enhancement. (A) Group forward phase poke efficiency, with no significant effect of NBOH treatment. Each day has 4 points plotted corresponding to each hour of the 4-h per day sessions. (B) Group forward phase percentage of correct trials, indicating no significant effect of NBOH treatment. (C) NBOH treatment significantly increased the number of reward pellets dispensed during the forward phase. (D) NBOH treatment significantly increased poke efficiency during the reversal phase compared to saline injection, indicating enhanced cognitive flexibility. (E) NBOH increases the percentage of correct trials. (F) NBOH treatment significantly increased the number of reward pellets dispensed during the reversal phase. Shaded regions represent standard error of the mean (SEM), linear regressions shown in pink for NBOH and black for saline; ns, not significant; $^{**}p < 0.01$; $^{****}p < 0.0001$.

start of the reversal protocol. Thus, our study focuses on the longer-term therapeutic effects of the psychedelic drug. It is important to distinguish such longer-term effects from immediate or short-lasting acute effects, that may be more related to the mind-altering impact of psychedelics and not to their longer-term therapeutic effects. In a two-choice visual discrimination task, 25CN-NBOH (1–2 mg/kg) was found to have no significant effects on reversal learning in mice when administered acutely, immediately before testing (46). Other previous rodent studies using attentional set-shifting and T-maze paradigms found impairment of flexible learning with acute administration of the psychedelics DOI (1 mg/kg) or 25CN-NBOH (1 mg/kg) on cognitive flexibility (53, 54). However, one study found acutely enhanced cognitive flexibility with acute psilocybin (1 mg/kg) in the same attentional set shifting paradigm that found impairment following administration of DOI (54). The differences in the acute effects of psychedelics on reversal learning may be due to the study design, discussed below, as well as a combination of drug and dose. DOI and 25CN-NBOH are much more potent (>10x) than psilocybin (41, 42, 47–49). Concentration-dependent acute suppression of working memory

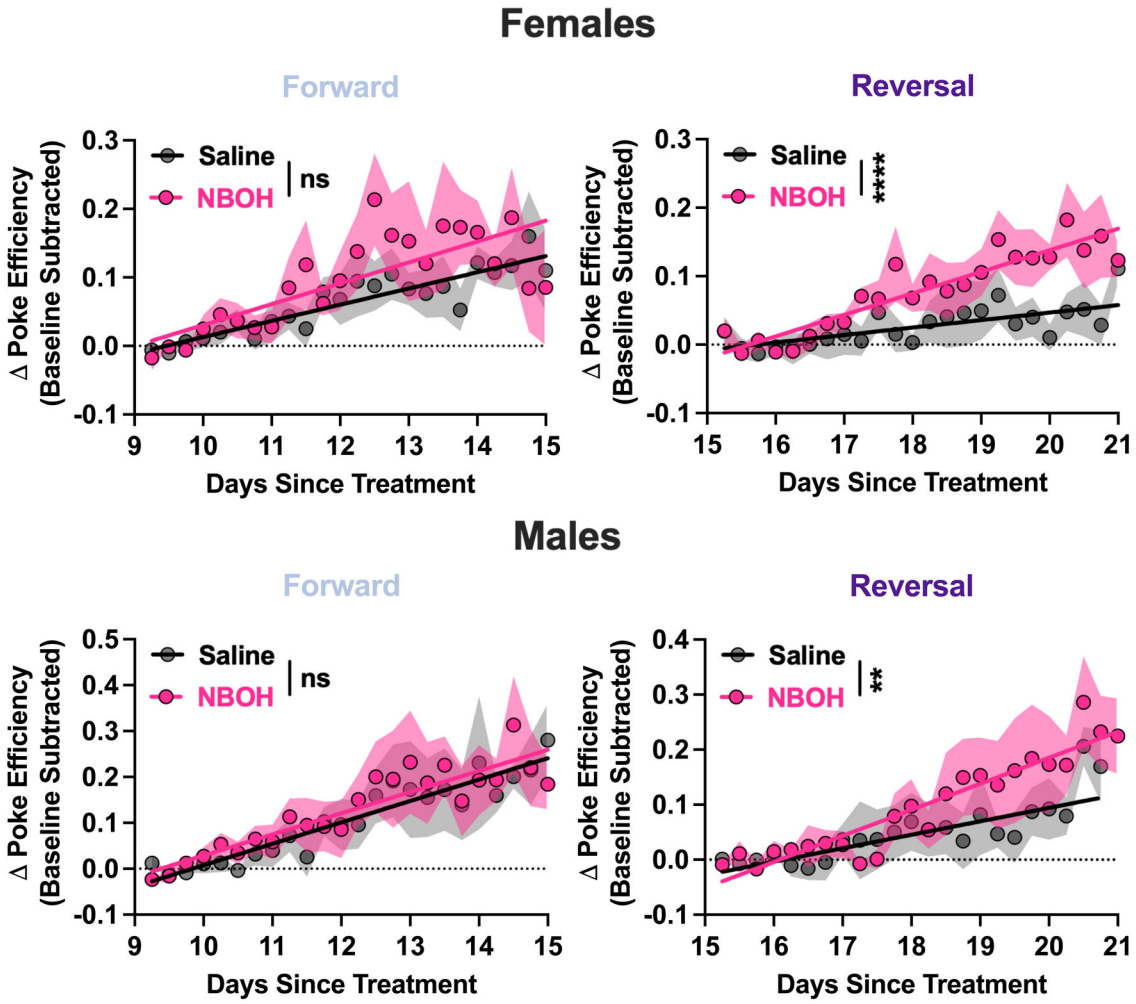


Figure 3. Lasting psychedelic enhancement of reversal learning ability in male and female mice. (Top) Forward and reversal phase changes to poke efficiency indicating NBOH treatment significantly improves reversal learning in female mice weeks after a single dose. (Bottom) Forward and reversal phase changes to poke efficiency in male mice indicating NBOH treatment significantly improves reversal learning weeks after a single dose. Shaded regions represent standard error of the mean (SEM), linear regressions shown in pink for NBOH and black for saline; ns, not significant; $^{**}p < 0.01$; $^{****}p < 0.0001$.

(27, 55–57) likely explains why the relatively less potent psychedelic psilocybin doesn't acutely impair behavioral performance at this dose. As the long-term effects of psychedelics on cognition are the effects that are more relevant therapeutically, it is important that future work continues to examine the sustained, in addition to acute, effects of psychedelics.

The current study also contrasts with previous studies in protocol design. We selected a reversal learning paradigm that is sufficiently complicated and somewhat easier to interpret compared to attentional set-shifting or T-maze paradigms. Two recent studies have also made use of reversal learning paradigms and have found long-term (study 1: 3 days; study 2: 14 days) positive effects of psychedelics on cognitive flexibility in female rats, but there are a few notable differences in behavioral protocols compared to the current study (51, 52). As opposed to conducting a sequential FR2-style task with only one reversal of the task, the 14-day long reversal study implemented an FR1 task that repeatedly reversed every 10 successful trials (51). While this study demonstrated that psilocybin increases the number of successes over time, it did not show if psilocybin improves accuracy, or if this is a function of increased trial initiations after psilocybin (51). Our FR2 style task with a single reversal after many days of training highlights the different effects psychedelics have on initial (forward) learning and reversal learning separately, which we would have otherwise been unable to do in a paradigm that frequently reverses. Our paradigm also likely results in fewer random successes that could inflate an animal's actual performance as we require precisely two sequential pokes in two separate holes. In addition, we conducted the task in both female and male mice. A similar study testing the long-term effects of DOI on reversal learning found that, depending on task structure, DOI has mixed effects on reversal learning ability (58). A week-long evaluation of initial learning after dosing appeared to assist in the enhancement of flexible learning, but if the animals were not exposed again to the task prior to reversal after dosing, DOI appears to have a negative effect on reversal learning ability. This finding suggests that further work needs to be done to evaluate what role practice following dosing has on cognitive flexibility.

In humans, psilocybin treatment has been found to improve cognitive flexibility up to 1 month after dosing (13, 14). However, these studies utilized a within-subject repeated measures design with no non-psilocybin control group (13), or with low dose psilocybin (1 mg) as the control group (14). Although promising, it is possible that behavioral performance was improved through familiarity with the task design rather than a direct result of the psychedelic treatment. It is currently unknown whether a single psychedelic dose would improve cognitive flexibility measured in a human study using independent measures.

PFC neurons have been shown to undergo spinogenesis and synaptogenesis after a single psychedelic administration through a pathway requiring 5-HT_{2A} receptor activation (23–31), but the precise mechanisms of 5-HT_{2A} receptor induced flexible learning and how long these benefits can last are still unknown. Here, we use 25CN-NBOH, which is 50–100x more selective for 5-HT_{2A} receptors over 5-HT_{2B} and 5-HT_{2C} receptors and has even weaker affinity for other 5-HT receptors (41, 42, 49). Future research into the long-term effects of other psychedelic drugs on cognitive flexibility will need to be conducted to examine whether psychedelics that target additional 5-HT receptor subtypes have similar long-lasting effects, or to determine whether the interaction with other 5-HT receptors abolishes the ability to enhance long-lasting flexibility. In addition, it remains unknown if non-hallucinogenic 5-HT_{2A} receptor agonists such as 2-bromo-LSD, lisuride, and 6-fluoro-diethyltryptamine (59–61), are also able to induce a lasting enhancement of flexible learning.

Psychedelic-mediated weeks-long enhancement of reversal learning ability allows for many further directions of research. Future studies will examine the effects that psychedelics have on mice across different ages. Additional studies will also determine the effects of different psychedelic drugs, dose levels, number of doses, or dose timing in this behavioral paradigm. While we did find an enhancement in a mouse model of cognitive flexibility with a 5-HT_{2A} receptor agonist, we did not use 5-HT_{2A} knockout mice to see if the absence of 5-HT_{2A} receptors would cause any deficits in this behavior, or if psychedelics would improve this behavior without the engagement of 5-HT_{2A} receptors.

A long-term positive psychedelic-induced enhancement of cognitive flexibility has several implications for future human psychedelic medicine, specifically for pathologies that involve deficits in executive function or synaptic loss. Cognitive flexibility is impaired in many disorders, including depression, PTSD, and Alzheimer's disease (AD) (62–64). While clinical trials evaluating the impact of psychedelic medicine on depression and PTSD are already underway and have shown promising results (13, 14), psychedelics have not yet been used to try to treat cognitive flexibility in AD and related neurodegenerative diseases. Additional research using mouse models of AD would be important to mechanistically demonstrate that psychedelics can indeed boost flexibility in these models and to confirm that psychedelics can also boost long-term synaptic activity in brain regions related to cognitive flexibility, such as the PFC in these same preclinical models. The task design presented here will facilitate future studies that can address these and other questions. This will allow for an even greater mechanistic understanding of the relationship between psychedelic treatment and cognitive flexibility.

Materials and Methods

Animals and Behavioral Apparatus

The open source, programmable FED3 device was used for all behavioral experiments. We programmed the FED3 via Arduino to deliver a 10 mg reward pellet if an animal successfully pressed the correct sequence of nose poke holes (left-then-right or right-then-left within 30 s, depending on the forward or reversal phase of the task). The reward pellets used in this study were 10 mg Bio-Serv Dustless Precision Pellets in the chocolate flavor. The cages used with the FED3 devices were modified standard mouse housing cages, with holes drilled into the front of the cage and magnets affixed to the cage's front to allow the animal to interact with the reward well and nose poke holes and ensure the device stays flush to the side of the cage during data collection. Data were collected within the animals' vivarium on a static shelf to minimize any effect of changing locations on stress and ensure ample room for both the cage and the device on the shelf. Each animal had their own experimentation cage and FED3 used for the duration of the experiment to minimize the stress of unfamiliar environment and odors. The animals' vivarium ran on a reversed light cycle with lights off (dark phase) from 7:00 AM to 7:00 PM. Each day, data were collected from approximately 10:00 AM to 2:00 PM, within the vivarium's dark phase. After each 4-h session, the animals were returned to their home cages until the next day. A total of 27 adult male and female C57BL/6 mice with a mean age of ~6 months were used in experiments, but the data from one mouse were excluded because the mouse did not interact with the FED3 device. All procedures were approved by the University of Michigan Committee on the Use and Care of Animals.

Procedure

Animals were injected intraperitoneally with either saline to function as a control ($N = 14$), or 25CN-NBOH ($N = 12$ mice) a 5-HT_{2A} receptor agonist, purchased from Tocris Bioscience, at a dose of 10 mg/kg (a dose previously shown to induce psychedelic-like effects in mice (44)), dissolved in sterile saline and brought up to a total volume less than 1% of the mouse weight. To allow the blinding of the main experimenter, these injections were done by another experimenter, and the main experimenter remained blinded until after the protocol had been completed. After injection, the animals were left to rest for 24 h in their home cage before beginning an 85% free feeding weight schedule for 2 days. During those 2 days, a few reward pellets were dropped into each animal's cage. This was done to ensure proper food motivation and acclimation to the pellets.

After 2 days of food restriction, animals were introduced to a training period to acclimatize to the FED3. After this point, most of the daily food was obtained through the FED3 device; chow was added to home cages supplementally as needed to maintain at least 85% free-feeding weight. However, most mice returned to free-feeding weight over the course of the full protocol. For 2 days, the animals underwent the habituation phase of the protocol, in which the animals were introduced to the FED3 and experimentation cages. Over the course of two separate 4-h sessions, the FED3 automatically delivered a reward pellet every 4 min and in response to any pokes to either nose poke hole. After the 2 days of habituation, the animals began fixed-ratio 1 (FR1) training phase in which a reward pellet would be delivered any time the mouse poked the left nose poke hole. Similarly, these sessions were 4 h long each and took place over the course of 3 days.

After the 5 days of training were completed, the mouse was then introduced to the sequential fixed-ratio 2 (SEQFR2)-forward and SEQFR2-reversal phases. To receive a reward pellet in the SEQFR2-forward phase, the animal must poke the left nose poke hole followed by the right nose poke hole within 30 s. Should the animal poke the right hole in isolation, the left hole twice in a row, or not follow a left poke with a right poke, the device entered a 10-s timeout phase in which no further pokes would be registered and any nose pokes during this timeout period were ignored. Like all other sessions, these sessions lasted for 4 h each over the course of 6 days. After those 6 days elapsed, the SEQFR2 rule was reversed, meaning the animal had to poke the right nose poke hole first followed by the left to receive a reward pellet. Like the forward phase, the reversal phase lasted for 6 days. After the protocol was completed, mice were returned to their normal feeding schedules, cages were cleaned and sanitized with Liquinox lab detergent, and FED3s were sanitized with 70% ethanol. The experimental timeline and protocol overviews are summarized in Figure 1.

Behavioral Analysis

In the SEQFR2 task, poke efficiency is the main measure of performance. This was calculated by finding the proportion of pellets dispensed out of all pokes carried out by the animal in each hour. As additional metrics of behavioral performance, we examined cumulative pellets dispensed over the course of each phase, as well as the proportion of correct trials initiated out of all trials ("percent correct"). Together, these three metrics reflect the absolute performance animals over the course of the task (cumulative pellets), as well performance relative to the amount of engagement with the device (poke efficiency and percent correct).

Statistics

Statistical procedures were performed with Prism GraphPad (version 10.3.0) and R. We conducted multiple linear regression analyses as our primary statistical method, which has also been used as the analysis method in other reversal learning paradigms (66–68). To ensure the robustness of our results, we conducted additional analyses by calculating each individual animal's regression curve and conducting Welch's one-sided t-tests to compare the saline and NBOH cohorts. Further statistical test information and significance are provided in the results section and figure legends.

Data Availability

Data generated in this study is available from the corresponding author upon reasonable request.

Acknowledgments

The authors thank all the members of the Ahmed lab for helpful discussions related to this project.

Author Contributions

Elizabeth Brouns acted as an investigator for this study. She conducted all the data collection, developed the task, contributed significantly to the writing of the final manuscript, generated figures, conducted preliminary analyses, managed data, and planned all animals run on this task. Tyler Ekins acted as an investigator for this study. He injected all mice to keep the main experimenter blinded, ran final statistical analyses, generated figures, and contributed significantly to the writing of this manuscript. Omar Ahmed was the principal investigator and senior author of this study, designed the study, developed the task, helped with planning the animals run on the task, contributed to figure design, and contributed significantly to the writing and editing of this manuscript.

Funding Sources

This work was supported by: NIH R01MH129282; NIH P50NS123067, NIH T32DA007268, University of Michigan Eisenberg Family Depression Center Eisenberg Scholar Award.

Author Disclosures

The authors declare no competing financial interest.

References

1. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa P, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. J Psychopharmacol. 2015;29(3):289–99. DOI: 10.1177/0269881114565144. PMID: 25586396
2. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017;43(1):55–60. DOI: 10.3109/00952990.2016.1170135. PMID: 27441452; PMCID: PMC5641975
3. Carhart-Harris RL, Bolstridge M, Rucker J, Day CMJ, Erritzoe D, Kaelen M, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016;3(7):619–27. DOI: 10.1016/S2215-0366(16)30065-7. PMID: 27210031
4. Sanches RF, de Lima Osório F, Dos Santos RG, Macedo LRH, Maia-de-Oliveira JP, Wichert-Ana L, et al. Antidepressant effects of a single dose of Ayahuasca in patients with recurrent depression: A SPECT Study. J Clin Psychopharmacol. 2016;36(1):77–81. DOI: 10.1097/JCP.0000000000000436. PMID: 26650973
5. Carhart-Harris RL, Roseman L, Bolstridge M, Demetriou L, Pannekoek JN, Wall MB, et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep. 2017;7(1):13187. DOI: 10.1038/s41598-017-13282-7. PMID: 29030624; PMCID: PMC5640601
6. Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl). 2018;235(2):399–408. DOI: 10.1007/s00213-017-4771-x. PMID: 29119217; PMCID: PMC5813086
7. Stroud JB, Freeman TP, Leech R, Hindocha C, Lawn W, Nutt DJ, et al. Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. Psychopharmacology (Berl). 2018;235(2):459–66. DOI: 10.1007/s00213-017-4754-y. PMID: 29085980; PMCID: PMC5813058
8. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol. 2018;8:974. DOI: 10.3389/fphar.2017.00974. PMID: 29387009; PMCID: PMC5776504
9. Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med. 2019;49(4):655–63. DOI: 10.1017/S0033291718001356. PMID: 29903051; PMCID: PMC6378413
10. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of psilocybin versus Escitalopram for depression. New Engl J Med. 2021;384(15):1402–11. DOI: 10.1056/NEJMoa2032994. PMID: 33852780
11. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of psilocybin-assisted therapy on major depressive disorder: A randomized clinical trial. JAMA Psychiatry. 2021;78(5):481–9. DOI: 10.1001/jamapsychiatry.2020.3285. PMID: 33146667; PMCID: PMC7643046
12. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. N Engl J Med. 2022;387(18):1637–48. DOI: 10.1056/NEJMoa2206443. PMID: 36322843
13. Doss MK, Považan M, Rosenberg MD, Sepeda ND, Davis AK, Finan PH, et al. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. Transl Psychiatry. 2021;11(1):574. DOI: 10.1038/s41398-021-01706-y. PMID: 34750350; PMCID: PMC8575795
14. Lyons T, Spriggs M, Kerkelä L, Rosas F, Roseman L, Mediano P, et al. Human brain changes after first psilocybin use. bioRxiv. 2024;2024.10.11.617955.
15. Cook SC, Wellman CL. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J Neurobiol. 2004;60(2):236–48. DOI: 10.1002/neu.20025. PMID: 15266654
16. Bondi CO, Rodriguez G, Gould GG, Frazer A, Morilak DA. Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by Chronic antidepressant drug treatment. Neuropsychopharmacology. 2008;33(2):320–31. DOI: 10.1038/sj.npp.1301410. PMID: 17406647
17. Chiba S, Numakawa T, Ninomiya M, Richards MC, Wakabayashi C, Kunugi H. Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(1):112–9. DOI: 10.1016/j.pnpbp.2012.05.018. PMID: 22664354
18. McKlveen JM, Morano RL, Fitzgerald M, Zoubovsky S, Cassella SN, Scheimann JR, et al. Chronic stress increases prefrontal inhibition: A mechanism for stress-induced prefrontal dysfunction. Biol Psychiatry. 2016;80(10):754–64. DOI: 10.1016/j.biopsych.2016.03.2101. PMID: 27241140; PMCID: PMC5629635
19. Qiao H, Li M-X, Xu C, Chen H-B, An S-C, Ma X-M. Dendritic spines in depression: what we learned from animal models. Neural Plast. 2016;2016:8056370. DOI: 10.1155/2016/8056370. PMID: 26881133; PMCID: PMC4736982
20. Negrón-Oyarzo I, Aboitiz F, Fuentealba P. Impaired functional connectivity in the prefrontal cortex: A mechanism for chronic stress-induced neuropsychiatric disorders. Neural Plast. 2016;2016:7539065. DOI: 10.1155/2016/7539065. PMID: 26904302; PMCID: PMC4745936
21. Jett JD, Bulin SE, Hatherall LC, McCartney CM, Morilak DA. Deficits in cognitive flexibility induced by chronic unpredictable stress are associated with impaired glutamate neurotransmission in the rat medial prefrontal cortex. Neuroscience. 2017;346:284–97.
22. Wellman CL, Bollinger JL, Moench KM. Effects of stress on the structure and function of the medial prefrontal cortex: Insights from animal models. Int Rev Neurobiol. 2020;150:129–53. DOI: 10.1016/bs.irn.2019.11.007. PMID: 32204829; PMCID: PMC9483990
23. Ly C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC, et al. Psychedelics promote structural and functional neural plasticity. Cell Rep. 2018;23:3170–82. DOI: 10.1016/j.celrep.2018.05.022. PMID: 29898390; PMCID: PMC6082376
24. Shao L-X, Liao C, Gregg I, Davoudian PA, Savalia NK, Delagarza K, et al. Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. Neuron. 2021;109(16):2535–44.e4. DOI: 10.1016/j.neuron.2021.06.008. PMID: 34228959; PMCID: PMC8376772
25. Cameron LP, Tombari RJ, Lu J, Pell AJ, Hurley ZQ, Ehinger Y, et al. A non-hallucinogenic psychedelic analogue with therapeutic potential. Nature. 2021;589(7842):474–9. DOI: 10.1038/s41586-020-3008-z. PMID: 33299186; PMCID: PMC7874389
26. de la Fuente RM, Zhu B, Guevara CA, Naler LB, Saunders JM, Zhou Z, et al. Prolonged epigenomic and synaptic plasticity alterations following single exposure to a psychedelic in mice. Cell Rep. 2021;37(3):109836. DOI: 10.1016/j.celrep.2021.109836. PMID: 34686347; PMCID: PMC8582597
27. Ekins TG, Brooks I, Kailasa S, Rybicki-Kler C, Jedrasiak-Cape I, Donoho E, et al. Cellular rules underlying psychedelic control of prefrontal pyramidal neurons. bioRxiv. 2023;2023.10.20.563334. DOI: 10.1101/2023.10.20.563334. PMID: 37961554; PMCID: PMC10634703
28. Cameron LP, Patel SD, Vargas MV, Barragan EV, Saeger HN, Warren HT, et al. 5-HT2ARs mediate therapeutic behavioral effects of psychedelic tryptamines. ACS Chem Neurosci. 2023;14(3):351–8. DOI: 10.1021/acschemneuro.2c00718. PMID: 36630260; PMCID: PMC9939288
29. Jefferson SJ, Gregg I, Dibbs M, Liao C, Wu H, Davoudian PA, et al. 5-MeO-DMT modifies innate behaviors and promotes structural neural plasticity in mice. Neuropsychopharmacology. 2023;48(9):1257–66. DOI: 10.1038/s41386-023-01572-w. PMID: 37015972; PMCID: PMC10354037
30. Vargas MV, Dunlap LE, Dong C, Carter SJ, Tombari RJ, Jami SA, et al. Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. Science. 2023;379(6633):700–6. DOI: 10.1126/science.adf0435. PMID: 36795823; PMCID: PMC10108900
31. Shao LX, Liao C, Davoudian PA, Savalia NK, Jiang Q, Wojtasiewicz C, et al. Psilocybin's lasting action requires pyramidal cell types and 5-HT_{2A} receptors. Nature. 2025; DOI: 10.1038/s41586-025-08813-6. PMID: 40175553
32. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167–202. DOI: 10.1146/annurev.neuro.24.1.167. PMID: 11283309
33. Kim C, Johnson NF, Cilles SE, Gold BT. Common and distinct mechanisms of cognitive flexibility in prefrontal cortex. J Neurosci. 2011;31(13):4771–9. DOI: 10.1523/JNEUROSCI.5923-10.2011. PMID: 21451015; PMCID: PMC3086290
34. Uddin LQ. Cognitive and behavioural flexibility: neural mechanisms and clinical considerations. Nat Rev Neurosci. 2021;22(3):167–79. DOI: 10.1038/s41583-021-00428-w. PMID: 33536614; PMCID: PMC7856857
35. Grant JE, Chamberlain SR. Impaired cognitive flexibility across psychiatric disorders. CNS Spectr. 2023;28(6):688–92. DOI: 10.1017/S1092852923002237. PMID: 37114560
36. Guarino A, Favieri F, Boncompagni I, Agostini F, Cantone M, Casagrande M. Executive functions in Alzheimer disease: A systematic review. Front Aging Neurosci. 2019;10:437. DOI: 10.3389/fnagi.2018.00437. PMID: 30697157; PMCID: PMC6341024
37. Bissonette GB, Powell EM. Reversal learning and attentional set-shifting in mice. Neuropharmacology. 2012;62(3):1168–74. DOI: 10.1016/j.neuropharm.2011.03.011. PMID: 21439304; PMCID: PMC3130808

38. Heisler JM, Morales J, Donegan JJ, Jett JD, Redus L, O'Connor JC. The attentional set shifting task: A measure of cognitive flexibility in mice. J Vis Exp. 2015;(96):51944. DOI: 10.3791/51944. PMID: 25741905; PMCID: PMC4354620
39. Hamilton DA, Brigman JL. Behavioral flexibility in rats and mice: Contributions of distinct frontocortical regions. Genes Brain Behav. 2015;14(1):4–21. DOI: 10.1111/gbb.12191. PMID: 25561028; PMCID: PMC4482359
40. Remmelink E, Smit AB, Verhage M, Loos M. Measuring discrimination- and reversal learning in mouse models within 4 days and without prior food deprivation. Learn Mem. 2016;23(11):660–7. DOI: 10.1101/lm.042085.116. PMID: 27918287; PMCID: PMC5066605
41. Hansen M, Phonekeo K, Paine JS, Leth-Petersen S, Begtrup M, Bräuner-Osborne H, et al. Synthesis and structure–activity relationships of N-benzyl phenethylamines as 5-HT2A/2C agonists. ACS Chem Neurosci. 2014;5(3):243–9. DOI: 10.1021/cn400216u. PMID: 24397362; PMCID: PMC3963123
42. Fantegrossi WE, Gray BW, Bailey JM, Smith DA, Hansen M, Kristensen JL. Hallucinogen-like effects of 2-([2-(4-cyano-2,5-dimethoxyphenyl) ethylamino]methyl)phenol (25CN-NBOH), a novel N-benzylphenethylamine with 100-fold selectivity for 5-HT2A receptors, in mice. Psychopharmacology (Berl). 2015;232(6):1039–47. DOI: 10.1007/s00213-014-3739-3. PMID: 25224567; PMCID: PMC4339409
43. Jensen AA, McCorvy JD, Petersen SL, Bundgaard C, Liebscher G, Kenakin TP, et al. Detailed characterization of the in vitro pharmacological and pharmacokinetic properties of N-(2-hydroxybenzyl)-2,5-dimethoxy-4-cyanophenylethylamine (25CN-NBOH), a highly selective and brain-penetrant 5-HT2A receptor agonist. J Pharmacol Exp Ther. 2017;361(3):441–53. DOI: 10.1124/jpet.117.239905. PMID: 28360333
44. Halberstadt AL, Sindhunata IS, Scheffers K, Flynn AD, Sharp RF, Geyer MA, et al. Effect of 5-HT2A and 5-HT2C receptors on temporal discrimination by mice. Neuropharmacology. 2016;107:364–75. DOI: 10.1016/j.neuropharm.2016.03.038. PMID: 27020041; PMCID: PMC5403251
45. Buchborn T, Lyons T, Knöpfel T. Tolerance and tachyphylaxis to head twitches induced by the 5-HT2A agonist 25CN-NBOH in mice. Front Pharmacol. 2018;9:17. DOI: 10.3389/fphar.2018.00017. PMID: 29467649; PMCID: PMC5808243
46. Odland AU, Kristensen JL, Andreasen JT. The selective 5-HT2A receptor agonist 25CN-NBOH does not affect reversal learning in mice. Behav Pharmacol.2021;32:448–52. DOI: 10.1097/FBP.0000000000000626. PMID: 33595957
47. Holze F, Singh N, Liechti ME, D'Souza DC. Serotonergic psychedelics: A comparative review of efficacy, safety, pharmacokinetics, and binding profile. Biol Psychiatry Cogn Neurosci Neuroimaging. 2024;9:472–89. DOI: 10.1016/j.bpsc.2024.01.007. PMID: 38301886
48. Poulie CBM, Jensen AA, Halberstadt AL, Kristensen JL. DARK classics in chemical neuroscience: NBOMes. ACS Chem Neurosci. 2019;11:3860–69. DOI: 10.1021/acschemneuro.9b00528. PMID: 31657895; PMCID: PMC9191638
49. Märcher-Rørsted E, Jensen AA, Kristensen JL. 25CN-NBOH: A selective agonist for in vitro and in vivo investigations of the serotonin 2A receptor. ChemMedChem. 2021;16(21):3263–70. DOI: 10.1002/cmdc.202100395. PMID: 34288515
50. Gargiulo AT, Hu J, Ravaglia IC, Hawks A, Li X, Sweasy K, et al. Sex differences in cognitive flexibility are driven by the estrous cycle and stress-dependent. Front Behav Neurosci. 2022;16:958301. DOI: 10.3389/fnbeh.2022.958301. PMID: 35990724; PMCID: PMC9386277
51. Fisher EL, Smith R, Conn K, Corcoran AW, Milton LK, Hohwy J, et al. Psilocybin increases optimistic engagement over time: computational modelling of behaviour in rats. Transl Psychiatry. 2024;14:394. DOI: 10.1038/s41398-024-03103-7. PMID: 39349428; PMCID: PMC11442808
52. Conn K, Milton LK, Huang K, Munguba H, Ruuska J, Lemus MB, et al. Psilocybin restrains activity-based anorexia in female rats by enhancing cognitive flexibility: Contributions from 5-HT1A and 5-HT2A receptor mechanisms. Mol Psychiatry. 2024;29:3291–304. DOI: 10.1038/s41380-024-02575-9. PMID: 38678087; PMCID: PMC11449803
53. Amodeo DA, Hassan O, Klein L, Halberstadt AL, Powell SB. Acute serotonin 2A receptor activation impairs behavioral flexibility in mice. Behav Brain Res.2020;395:112861. DOI: 10.1016/j.bbr.2020.112861. PMID: 32814148
54. Pacheco AT, Olson RJ, Garza G, Moghaddam B. Acute psilocybin enhances cognitive flexibility in rats. Neuropsychopharmacology.2023;48:1011–20. DOI: 10.1101/2023.01.09.523291. PMID: 36712091; PMCID: PMC9881983
55. Pokorny T, Duerler P, Seifritz E, Vollenweider FX, Preller KH. LSD acutely impairs working memory, executive functions, and cognitive flexibility, but not risk- based decision-making. Psychol Med. 2020;50:2255–64. DOI: 10.1017/S0033291719002393. PMID: 31500679
56. Frederick DL, Gillam MP, Lensing S, Paule MG. Acute effects of LSD on Rhesus monkey operant test battery performance. Pharmacol Biochem Behav. 1997;57:633–41. DOI: 10.1016/s0091-3057(96)00469-8. PMID: 9258988
57. Bouso JC, Fábregas JM, Antonijoan RM, Rodríguez-Fornells A, Riba J. Acute effects of ayahuasca on neuropsychological performance: Differences in executive function between experienced and occasional users. Psychopharmacology (Berl). 2013;230:415–24. DOI: 10.1007/s00213-013-3167-9. PMID: 23793226
58. Šabanović M, Lazari A, Blanco-Pozo M, Tisca C, Tachrount M, Martins-Bach AB, et al. Lasting dynamic effects of the psychedelic 2,5-dimethoxy-4- iodoamphetamine ((±)-DOI) on cognitive flexibility. Mol Psychiatry. 2024;29:1810–23. DOI: 10.1038/s41380-024-02439-2. PMID: 38321122; PMCID: PMC11371652
59. Faillace LA, Vourlekis A, Szara S. Clinical evaluation of some hallucinogenic tryptamine derivatives. J Nerv Ment Dis. 1967;145:306–13. DOI: 10.1097/00005053-196710000-00005. PMID: 6076017
60. González-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, et al. Hallucinogens recruit specific cortical 5-HT2A receptor-mediated signaling pathways to affect behavior. Neuron. 2007;53:439–52. DOI: 10.1016/j.neuron.2007.01.008. PMID: 17270739
61. Lewis V, Bonniwell EM, Lanham JK, Ghaffari A, Sheshbaradaran H, Cao AB, et al. A non-hallucinogenic LSD analog with therapeutic potential for mood disorders. Cell Rep. 2023;42:112203. DOI: 10.1016/j.celrep.2023.112203. PMID: 36884348; PMCID: PMC10112881
62. Maramis MM, Mahajudin MS, Khotib J. Impaired cognitive flexibility and working memory precedes depression: A rat model to study depression. Neuropsychobiology. 2020;80(3):225–33. DOI: 10.1159/000508682. PMID: 32712605; PMCID: PMC8220918
63. George SA, Rodriguez-Santiago M, Riley J, Abelson JL, Floresco SB, Liberzon I. Alterations in cognitive flexibility in a rat model of post-traumatic stress disorder. Behav Brain Res. 2015;286:256–64. DOI: 10.1016/j.bbr.2015.02.051. PMID: 25746511
64. Guarino A, Forte G, Giovannoli J, Casagrande M. Executive functions in the elderly with mild cognitive impairment: A systematic review on motor and cognitive inhibition, conflict control and cognitive flexibility. Aging Ment Health. 2019;24(7):1028–45. DOI: 10.1080/13607863.2019.1584785. PMID: 30938193
65. Tyler E, Kravitz L. Mouse at feeder. DOI: 10.5281/zenodo.3926026.
66. D'Agostini M, Burger AM, Franssen M, Claes N, Weymar M, von Leupoldt A, et al. Effects of transcutaneous auricular vagus nerve stimulation on reversal learning, tonic pupil size, salivary alpha-amylase, and cortisol. Psychophysiology. 2021;58(10):e13885. DOI: 10.1111/psyp.13885. PMID: 34245461
67. Grossman CD, Bari BA, Cohen JY. Serotonin neurons modulate learning rate through uncertainty. Curr Biol. 2022;32(3):586–99.e7. DOI: 10.1016/j.cub.2021.12.006. PMID: 34936883; PMCID: PMC8825708
68. Chidambaram S, Wintergerst S, Kacelnik A, Nachev V, Winter Y. Serial reversal learning in nectar-feeding bats. Anim Cogn. 2024;27(1):24. DOI: 10.1007/s10071-024-01836-y. PMID: 38451365; PMCID: PMC10920430

Genomic Press

Where Breakthrough Science Meets Clinical Impact

At Genomic Press, we advance the frontiers of neuroscience and psychiatry:

- **Multidisciplinary Scope: From molecular mechanisms to clinical applications**
- **Varied Research Welcome: We publish genomic and non-genomic papers**
- **Expert Editorial Boards: Led by distinguished researchers**
- **Rapid Publication: Streamlined review process without sacrificing quality**
- **Global Visibility: Reaching researchers and clinicians worldwide**

Recent publications cover topics such as the economic and public health implications of psychedelic therapies, the effects of ayahuasca on fear and anxiety, psychedelic treatment for anorexia nervosa and body dysmorphic disorder, and advancements, challenges, and future directions for treating resistant depression with psilocybin-assisted psychotherapy.

Genomic Press

A PARADIGM SHIFT IN RESEARCH PUBLISHING

Our mission: Transforming scientific publishing through author-focused support and global dissemination.

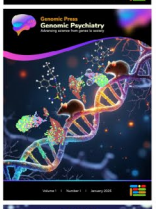
Our fair-cost platform delivers rapid, rigorous review and uses contemporary tools to amplify research visibility worldwide.

We welcome scientists across disciplines, providing emerging research unprecedented exposure. Our three journals now feature over 100 published papers with extraordinary global reach.

Our innovative dissemination strategy has generated 4,000+ news stories in 35+ languages worldwide. Through strategic partnerships with respected science communication platforms like EurekAlert! (AAAS) and targeted social media campaigns, with 2M+ views, we have created unprecedented visibility for our authors' work, connecting cutting-edge research directly with global audiences.

Brain Medicine

From Neurons to Behavior and Better Health. The premier journal that integrates fundamental science and translation across all brain disciplines.



Genomic Psychiatry

Advancing Science from Genes to Society. A journal for cutting-edge research spanning genes, molecules, circuits, behavior, and public health.

Psychedelics

The Journal of Psychedelic and Psychoactive Drug Research. A trailblazing platform for advancing research into science, medicine, and culture.

Join our thriving community of researchers charting new territories in genomic psychiatry, brain medicine, and psychedelic and psychoative drug research

Welcome to the future of scientific publishing!