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Cover Art

Cover Image: Psilocybin-containing mushrooms and the systematic evidence for treating obsessive-compulsive behaviors. This issue's cover features *Psilocybe cubensis* mushrooms, displaying the characteristic blue bruising from psilocin oxidation. The image accompanies the systematic review by Gattuso and colleagues, which synthesizes clinical and preclinical evidence demonstrating that psilocybin produces consistent reductions in obsessive-compulsive behaviors. In clinical studies, single doses led to rapid symptom reductions persisting for weeks. In SAPAP3 knockout mice, a validated genetic model of compulsive behavior, single psilocybin administration produced robust, enduring reductions in excessive grooming, independently replicated across laboratories. These convergent findings across species point toward common neural mechanisms in cortico-striatal circuits, with implications for novel treatments across the obsessive-compulsive and related disorders spectrum. The systematic review by Gattuso et al. (pages 15–31) is discussed in the accompanying editorial by Licinio and Wong (pages 1–3).

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EDITORIAL

From compulsive behaviors to psychedelic therapeutics: When mice and man speak the same circuit language

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Introduction: The inability to stop

"I couldn't stop." Just four words, but those with obsessive–compulsive disorder repeat them like a mantra: a confession, an apology, an explanation that explains nothing.

The hand-washing continues despite bleeding skin. People keep checking things, even when they know there is no need to: like the stove is off, the door is locked, the symmetry is checked. What does the neurobiology behind this inability to inhibit entail?

For many decades, psychiatry has sought the biological anchors of compulsive behavior, running various neuroimaging suites, scouring genetic databases, and perhaps most productively, closely observing the mice that groom themselves raw. The review by Gattuso et al. in this issue represents an increasingly rare event in the current neuroscience landscape: translational convergence; preclinical models and clinical observations direct towards the same neural territory. Although we are not there yet, it indicates that we have found a target that is a valid therapeutic option (1).

A different narrative

The article draws on evidence from four clinical trials and nine preclinical trials into the effects of psilocybin on obsessive and compulsive behaviors (Figure 1). The usual psychedelic research story does not come out. Psilocybin can both cure depression and induce a mystical experience. A much more mechanistically engaging narrative about cortico-striatal circuits, behavioral inhibition, and the possibility that serotonergic psychedelics might modulate compulsivity via distinct pathways from their effects on mood.

This matters.

Obsessive-compulsive disorder often does not respond adequately to frontline treatment or medications, and it afflicts two to three percent of the population. However, there is more to it than that. Compulsive behavior is a dimension that cuts across diagnostic boundaries. It manifests in addiction, eating disorders, body dysmorphic disorder, Tourette syndrome, and even the rigid cognitive patterns of the autism spectrum conditions.

The translational achievement: Cross-laboratory replication

This translational success is of special interest. Laboratory studies in Israel and Australia, and later validation studies, have independently observed a remarkable finding in SAPAP3 knockout mice: a single dose of psilocybin produces sustained anti-grooming effects for 1-7 weeks (2, 3). To put this finding in context, these mice are genetically engineered to lack the protein SAPAP3 (a postsynaptic scaffolding molecule highly expressed in the striatum), and groom themselves excessively (to the point of self-harm). Critically, this excessive grooming in mice is accompanied by cortico-striatal dysfunction, which models the circuit-level dysfunction found in humans with obsessive-compulsive disorder (4). When independent laboratories observe the same therapeutic effect in the same genetic model, using different doses and assessment timepoints, neuroscience takes notice. Preclinical psychopharmacology is a field where replication is now the exception rather than the rule.

This collaboration between labs matters because it addresses the reproducibility crisis in behavioral neuroscience. Too often, one exciting result creates a new subfield that later collapses with a wave of failed replications. We have independent teams here, asking similar questions, using similar methods, getting similar answers.

Bidirectional flow: From bedside to bench and back

What makes this systematic review truly translational is the smooth two-way flow of insights between the bedside and the bench. The clinical observations came first. This pioneering study, reported in 2006 by Moreno and colleagues, found that single doses of psilocybin rapidly reduced obsessive-compulsive symptoms in nine patients with treatment-resistant OCD. Specifically, the effects were observed between four and twenty-four hours post-administration (5). More recently, Schneier and colleagues found that a 25 mg dose significantly reduced symptoms of body dysmorphic disorder at multiple time points, extending to 12 weeks, with large effect sizes (6). In the most methodologically sophisticated clinical study to date, Pellegrini and colleagues found that 10 mg psilocybin rapidly reduced symptoms in adults with moderate-to-severe OCD. In that study, compulsions improved more robustly than obsessions (7).

Among the plethora of notable clinical observations, one issue has crossed researchers' minds that only preclinical work can answer: are these effects genuine pharmacological phenomena, or due to placebo, expectancy, and extensive psychological support given during any psychedelic trial? The answer from rodent studies is unambiguous. Mice have no expectations about psychedelic therapy. They receive no preparatory therapy, no integration sessions afterward, no cultural narratives about mystical experiences catalyzing personal transformation. Yet, the anti-compulsive effects appear robust.

This tells us something important: the biological substrate matters. The way psilocybin works in reducing compulsive behaviors is likely to be more than mere suggestion and more than the subjective psychedelic experience.

The mechanistic mystery: Beyond 5-HT2A

So, what is the mechanism that makes this an interesting story and not just an uplifting one? Research has shown that the anti-compulsive actions of psilocybin can be achieved without 5-HT2A receptor activation. Gattuso and colleagues highlight this in multiple studies (8, 9). In other words, the main target thought to mediate the psychedelic experience is not responsible for these effects. What's more, when researchers pretreated animals with selective 5-HT2A antagonists that completely block these hallucinogenic-like behaviors, there remains a reduction in compulsive behaviors. According to this finding, which multiple research groups have replicated, we may have pharmacological agents that act via different mechanisms.

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Figure 1. From compulsive behaviors to potential therapeutic interventions. (A) Excessive hand-washing illustrating compulsive behaviors characteristic of obsessive-compulsive disorder. (B) *Psilocybe cubensis* mushrooms containing psilocybin, showing characteristic blue bruising from psilocin oxidation. Psilocybin is under investigation for the treatment of obsessive-compulsive and related disorders. Images © Depositphotos.

The 5-HT2A receptor has become too central to the field. Everything psychedelic is attributed to it, which makes no sense. The present evidence suggests otherwise. Psilocybin may diminish compulsivity via 5-HT2C receptor effects, modulation of striatal glutamatergic signaling, actions on BDNF pathways, or mechanisms yet to be conceived. The uncertainty here is not a weakness but an opportunity. When blocking the presumed mechanism of action does not block the therapeutic effect, the molecule provides us with new insights into how the brain works.

Practical implications: Scalability without the trip

One practical implication deserves emphasis. If the anti-compulsive effects work independently of 5-HT2A activation, they could work in a setting that does not require the heavy-duty psychedelic experience that today mandates clinic oversight, special setting, and hours of therapist time. Kiilerich et al. observed that multiple doses of psilocybin below the hallucinogenic threshold decreased grooming behavior in rats while increasing synaptic markers in the paraventricular thalamus of the same species (10). This raises the question of whether treatment paradigms can be developed that retain therapeutic efficacy while eliminating the subjective effects that limit scalability and accessibility.

Methodological honesty: Acknowledging limitations

However, we must temper enthusiasm with methodological honesty. The limitations of the clinical studies described here are common. The three main trials involved only 9, 12, and 19 participants, a small sample size. Most clinical trials did not include a placebo control group. The retrospective survey conducted by Buot et al. among 135 psilocybin mushroom consumers is subject to the selection bias inherent in web-based self-report (11). Most troublesome is the blinding issue: when a drug induces drastic changes in consciousness, participants know whether or not they received the active drug. Even sophisticated active placebos cannot mimic the subjective psychedelic effects. The contribution of expectancy and placebo to the observed effects is yet to be quantified.

Preclinical literature methodology tends to be stronger; however, it has its own translational issues. Rodents can model compulsions (behaviors), but they cannot model obsessions (thoughts, ruminations, mental compulsions). According to the Pellegrini clinical data, it appears that although obsessions showed less improvement, compulsions were addressed more effectively (7). Most probably, psilocybin exerts a beneficial effect on the cortico-striatal circuitry of the brain. This plays a relevant role in selecting patients and in setting realistic expectations for outcomes.

Studies on mice and humans have shown temporal discrepancies. In rodent models, single-dose effects persist for weeks. In humans, benefits begin to fade within one to four weeks. Why? Do mice not have the ongoing psychological stressors, relationship problems, workplace issues, and existential questions that keep sustaining symptomatology in humans? Or do the measurement instruments differ in sensitivity? It is also possible that the compulsive grooming observed in SAPAP3 mice is a more pure neurobiological phenomenon than the complex psycho-social-biological entity known as OCD we diagnose in our human patients.

The road ahead: A clear research agenda

Where does this leave the field? According to the systematic review by Gattuso and colleagues, a clear research agenda emerges from a genuine confrontation with limitations. There is a need for randomised controlled trials with sample sizes sufficient to detect clinically meaningful effects and exclude placebo effects. The ongoing study by Ching et al. (planned enrollment of 36 participants with OCD, using niacin as an active placebo, psychedelic-naive participants) is the next methodological generation study (12). We need mechanistic neuroimaging studies exploring how psilocybin alters cortico-striatal connectivity and whether normalization of circuit hyperactivity predicts symptom response. We require studies that optimize doses for comparison. We may, therefore, most urgently require studies that properly include sex as a biological variable, as evidence emerges of sex-specific psilocybin responses.

We also require something equally important yet more difficult to implement: studies that test psilocybin across the entire range of compulsive disorders. The Schneier research into body dysmorphic disorder is a beginning (6). And then what of trichotillomania, dermatillomania, and hoarding disorder? The compulsive drug-seeking of addiction, the repetitive behavioral patterns in autism, the motor and vocal tics of Tourette syndrome—what about these? If psilocybin really does modulate a transdiagnostic dimension of compulsivity, then cross-testing in these disorders would reveal if we have identified a core mechanism or just a disorder-specific effect.

Conclusion: A legitimate starting point

The translational paradigm offered in this review is a model for how psychedelic science can evolve beyond its present state of small open-label trials and enthusiastic testimonials. Clinical observations generate hypotheses. Preclinical models evaluate mechanisms in settings that eliminate confounders. Understanding mechanics helps to develop more advanced clinical trials. Each domain checks the other's limitations. Each domain answers questions that the other cannot address. This iterative, bidirectional process is how pharmacology advances from serendipitous observation to rational therapeutics.

We began with patients who could not stop. We end with mice that also could not stop, until a single dose of a compound changed something in their striatum, allowing behavioral flexibility to return. The distance between mouse and human remains vast, spanning chasms of consciousness, subjectivity, and social context that no amount of circuit mapping

can fully bridge. Yet, when both species share the same neural architecture and respond to the same molecule in ways that parallel each other, science has found a handhold. Not certainty. Not cure. But a legitimate starting point for the careful work of translation.

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INNOVATORS & IDEAS: RISING STAR

Erin Mauney: Psychedelics as modulators of the gut-brain interaction

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Keywords: Psilocybin, gastroenterology, interoception, IBS, pain, trauma

Dr. Erin E. Mauney serves as Assistant Professor of Pediatrics (Gastroenterology) at Tufts University while maintaining a research appointment at Massachusetts General Hospital. With dual board certification, including obesity medicine, she integrates clinical expertise with innovative research at the intersection of gut-brain disorders and psychedelic medicine. Dr. Mauney's groundbreaking work explores how psilocybin modulates interoception in treatment-resistant IBS, the first study of its kind in gastroenterology. In this Genomic Press Interview, she articulates how early-life trauma becomes somatically encoded and how psychedelic-assisted therapy creates pathways for emotional release and functional improvement. Her patient-centered approach combines neuroimaging, qualitative analysis, and clinical outcomes to develop scalable therapeutic options that challenge the artificial mind-body divide in contemporary medicine. Dr. Mauney's research represents a paradigm shift in understanding how psychedelics may transform treatment for the significant population of patients who remain unresponsive to conventional therapies.

Part 1: Erin Mauney – 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 interested in science from a young age; my mother recounts that at age 4, I kept "experiments"—small containers of flour, sugar, and water—hidden throughout the house and guarded them jealously as I watched bacteria and mold bloom on the surface. I briefly thought about channeling my love for argument and rhetoric into law, but ultimately became fascinated by neuroscience and how our brain and body communicate constantly.

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

I have maintained this interest in bacteriology, as I was drawn to gastroenterology in part due to its emphasis on understanding and modulating the unfathomably vast microbial world inside of us. In fellowship, I conducted basic science research in the lab of Dr. Kostic on bacteria that help induce immune tolerance. In my clinical life, I love that GI is such an integrative field and that addressing GI disorders requires understanding the patient's psychosocial background, resources (e.g., access to healthy food), and daily life. During my medical training, I became aware of how common trauma, especially early life trauma, unfortunately is in the human experience. Although there is more discussion in pediatrics about the cumulative effects of toxic stress over the lifespan, I think overall this is an area that medicine, particularly gastroenterology and obesity medicine, really fails to understand and address meaningfully.

Figure 1. Erin Mauney, MD, Tufts University, USA.

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 had read a bit about ayahuasca in undergraduate coursework, but like so many people, my entry point into psychedelics was with reading Michael Pollan's "How to Change Your Mind." I read this during the pandemic as I officially decided to enter pediatric gastroenterology as a field. I have also been reading primary psychodynamic literature to understand early life's

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impact on mind-body disorders, such as "Theaters of the Body" by Joyce McDougall. I was also significantly influenced by Winnicott's work on play and playfulness in therapy and healing – he was a psychoanalyst and pediatrician, similarly interested in how early life shapes people. Putting together these thoughts with the patients and families I have taken care of over the years with very entrenched, challenging somatic symptoms without apparent cause, many of whom had suffered horrific abuse, I became very interested in the applicability of this emerging (or perhaps more apt to say, re-emerging) field of psychedelic-assisted medicine to patients who seem to be at war with their bodies.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?
I did not get into my top choice of pediatric gastroenterology fellowship. I applied to stay at my residency institution, Boston Children's Hospital, but was matched across town at Massachusetts General Hospital instead. This felt like quite a blow and a personal failure at the time! However, I had an incredible fellowship experience and gained access to many mentors, including Dr. Franklin King at the Center for the Neuroscience of Psychedelics and Dr. Brad Kuo at the Center for Neurointestinal Health, whom I would have never worked with had I gotten what I thought I wanted.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
Cultivating honest, genuine relationships with each person you work with, whether your subordinate or your superior, is critical to effective work. It is important, but not easy, to bring your whole self to work and to create an environment that allows others to do the same. It also makes being at work a lot more fun! Beyond that, being meticulous, paying attention to detail, and moving forward on decisions that need your input quickly are key, especially in the dynamic field of clinical research.

Please tell us more about your current scholarly focal points within your chosen field of science.
I am interested in how psychedelics like psilocybin can modulate interoception, or how people perceive their body, and specifically their GI symptoms. Our current study, in which patients with refractory IBS are given two doses of psilocybin and associated therapy pre- and post-dosing, is the first psychedelic study within the field of gastroenterology. I am interested in how to optimize psychedelic therapy and bring it to the clinic at scale. I would love to one day study this more mechanistically and from a basic science perspective, e.g., in model organisms, but right now my research is focused on both patient-reported outcomes (e.g., abdominal pain), qualitative patient reflections on the experience, and neuroimaging correlates via fMRI.

What impact do you hope to achieve in your field by focusing on specific research topics?
This study brings a new option for patients who have not been helped by any existing approaches to IBS (which may be 60%+ of patients by some studies!) I also hope that, in a broader sense, this work helps heal the schism between mind and body that so many physicians practice within.

What do you most enjoy in your capacity as an academic or research rising star?
It has been very fun to share the preliminary results of our work with other doctors and scientists and to be inspired by their approaches to psychedelic therapy. On a personal level, I enjoy the complex, fast-paced work of early-stage clinical research. It is a different skill set than what I use to see patients or perform endoscopy, but it is gratifying to see all of the small decisions you make add up to a big study with exciting data.

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?
Although my research is primarily with adult subjects, working in pediatrics means witnessing the injustice and inequality in our society every day. I am deeply interested in pediatric obesity prevention and treatment. Adequately addressing this cause will require a full-scale realignment of our society's priorities, including in the food we subsidize and then feed to our children, the car-centric nature of our cities, the focus in schools on sitting and performing academically, the degree to which we allow social media and other tech companies to denigrate childhood in order to make money, and beyond.

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 two young children, my husband, and my dog, exploring Boston's many parks, which are little gems throughout the city.

Part 2: Erin Mauney – Selected questions from the Proust Questionnaire.[1]

What is your most marked characteristic?
Persistence.

Among your talents, which one(s) give(s) you a competitive edge?
Persistence again – the refusal to take no for an answer when I really want something ☺.

If you could change one thing about yourself, what would it be?
Increased self-compassion and acceptance.

What is your current state of mind?
Hopeful and excited about science, worried about the state of the world.

What is your idea of perfect happiness?
I love the feeling of hanging out with family after a day of productive writing and a nice long run in the sunshine.

When and where were you happiest? And why were so happy then?
Now, after finishing medical training and having more self-determination about how I spend my time and structure my days.

What is your greatest fear?
Losing my kids.

What is your greatest regret?
Not being more open and loving with the people I care for.

[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. Spring arrives in Boston.

What are you most proud of?
My family.

What do you consider your greatest achievement?
Giving my children a loving, warm, and secure childhood.

What or who is your greatest passion?
Restoring humanity to the practice of medicine.

What is your favorite occupation (or activity)?
Long, contemplative walks in the Boston spring (see Fig. 2).

What is your greatest extravagance?
Travel.

What is your most treasured possession?
We just bought our first house, so I will go with that.

Where would you most like to live?
Scandinavia, Portugal, or Costa Rica.

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

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

What do you consider the most overrated virtue?
Restraint.

What do you most value in your friends?
Sense of humor, steadiness.

Which living person do you most admire?
No one person, but bits and pieces of so many.

Who are your heroes in real life?
Some people have much less comfortable lives than I do, yet show up every day with a good attitude and a desire to give their best and ease others' load.

If you could have dinner with any historical figure, who would it be and why?
Mr. Rogers – such a deep understanding of and compassion for children (and the children within each of us).

Who are your favorite writers?
Mary Olliver, Ed Yong, Richard Powers, Elena Ferrante, Robin Wall Kimmer, and Catherine Newman.

Who are your heroes of fiction?
I have two: Jonas from Lois Lowry's *The Giver*, a boy who risks everything to escape his emotionless dystopian society after being chosen to receive its suppressed memories, and Demon Copperhead from Barbara Kingsolver's novel *Demon Copperhead*, a modern Appalachian retelling of Charles Dickens's *David Copperfield*, who survives foster care and the opioid crisis with remarkable resilience. Both characters face broken systems with moral courage that I deeply admire.

What aphorism or motto best encapsulates your life philosophy?
We are what we repeatedly do.

Boston, Massachusetts, USA
12 May 2025

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Psychedelics

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INNOVATORS & IDEAS: RESEARCH LEADER

Claire Foldi: Unravelling the neurobiology of eating disorders to inform effective treatments

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Keywords: Anorexia nervosa, eating disorders, animal models, neural circuits, cognition, psychedelics

Dr Claire J. Foldi is an Associate Professor in the Department of Physiology at Monash University, where she leads a multidisciplinary research program investigating the brain circuits that drive anorexia nervosa and other eating disorders. Her work bridges preclinical neuroscience with translational relevance, offering critical insight into the biological mechanisms that underlie psychiatric illness. She is a founding member of the executive of the Australian Eating Disorders Research & Translation Centre (AEDRTC). This role requires extensive collaboration and knowledge exchange with clinicians, service providers, and individuals with lived experience. These positions ensure that her research is both scientifically rigorous and socially relevant. With eating disorders affecting millions and remaining among the most fatal yet poorly understood mental illnesses, Dr Foldi's research addresses a pressing gap: how disruptions in brain pathways involved in reward, self-control, and decision-making contribute to the persistence of disordered eating. Her lab uses advanced neural recording and manipulation tools to map these circuits and explore how novel therapeutics, including psychedelics, may modulate them. Widely recognized for her rigorous yet exploratory approach, Dr. Foldi actively integrates techniques and perspectives from adjacent fields to push the boundaries of eating disorders research. In this Genomics Press interview, she reflects on her unexpected path into the field and how early experimental observations, combined with the rising interest in psychedelic medicine, have positioned her as a leading voice in a new generation of research at the intersection of metabolism, neurobiology, and psychiatry.

Part 1: Claire J. Foldi – Life and Career

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

I have always been fascinated by human behaviour and how the brain processes experiences, such as perception, emotion, and belief. A pivotal moment was an undergraduate psychology course on pathological thinking that inspired me to study why some people experience unusual thoughts. The most unusual I could imagine, at the time, was the hallucinations and delusions experienced by people living with schizophrenia, and I pursued a PhD that aimed to explore the biological bases of social and environmental risk factors for schizophrenia. This experience sparked my deep interest in the biology underlying mental illness, in particular, the interactions between biology and social and cultural factors. It also gave me the toolkit I still draw on today: curiosity, rigour, and an appreciation for how much we still do not know.

Figure 1. Claire J. Foldi, PhD, Monash University, Australia.

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

Ironically, I did not set out to become a specialist in eating disorders or psychedelics research. While my early training focused on schizophrenia, over time, I became increasingly interested in how behaviours like reward insensitivity, cognitive rigidity, and compulsivity overlapped across many seemingly disparate psychiatric conditions. That curiosity led me to models of anorexia nervosa and eventually to explore how compounds like psilocybin might help address entrenched behavioural patterns that don't respond to current treatments. So, while the research direction was not pre-planned, it was driven by following the science—and being willing to pivot when unexpected opportunities and questions arose.

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

I have had a fairly organic trajectory: each step opened new doors I had not anticipated. A defining moment came when I was awarded two major

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independent grants, back-to-back, that allowed me to pursue research I never expected I would dedicate my life to, even in my wildest dreams. That autonomy encouraged me to think more boldly about research design and to start mentoring students. I soon realized that building a lab was not just about research; it was about people. Founding the Foldi Lab at Monash has enabled me to create a space where early-career researchers can thrive and where unconventional research questions, such as those involving psychedelics, can be pursued rigorously and creatively.

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?

At one point, I agreed to a side project on the neuronal control of body weight that seemed peripheral to my research interests at the time. I worried I was losing focus and my career trajectory would falter. However, that side project became the seed for my current research program in eating disorders. It taught me the value of exploratory work and being open to deviation from linear goals. Some of the most impactful parts of my career have come from following unexpected leads with an open mind.

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

Three values stand out: intellectual honesty, collaboration over competition, and a commitment to mentoring. I had great mentors who encouraged critical thinking, and that is a culture I have tried to foster in my lab. I also firmly believe that research should be rigorous but not rigid. Our lab environment encourages curiosity, innovation, and co-designed projects with students and collaborators.

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

My lab investigates how internal states like hunger and anxiety interact with brain circuits that govern "higher order" cognitive behaviours. We utilize cutting-edge tools, such as in vivo fibre photometry and computational behavioural modelling, to investigate how brain dynamics influence decisions regarding food, threat, and reward. This includes studying the neural basis of anorexia nervosa and evaluating how novel therapeutics like psilocybin may help restore behavioural flexibility. We also explore how early-life adversity (like adolescent food insecurity) biologically embeds risk for binge eating and compulsivity.

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

I want to shift how we understand and treat eating disorders, moving beyond surface symptoms to the underlying neurobiology. By identifying the brain circuits and mechanisms that drive persistent behaviours, I aim to help develop more targeted and effective treatments. I also want to contribute to a more nuanced understanding of psychiatric illness, one that respects both biological and lived experience perspectives.

Eating disorders are among the most devastating and least understood mental health conditions. In Australia alone, over 1.1 million people, approximately 4.5% of the population, are currently living with an eating disorder, and 10.5% will experience one at some point in their lives. These conditions carry the highest mortality rate of any psychiatric illness, with 1,273 deaths recorded in 2023. Despite their prevalence and severity, treatment outcomes remain poor. Less than one in three individuals affected reach out for help, and even among those who do, relapse rates are high, and full recovery is elusive for many. The ripple effects extend beyond individuals to families, workplaces, and the broader economy. Eating disorders cost the Australian economy $18.1 billion annually in lost productivity, healthcare expenses, and other associated costs.

My research aims to address these challenges by unravelling the neural mechanisms underlying eating disorders. This includes exploring novel therapeutics, such as psychedelics, which may offer new avenues for treatment-resistant cases. Ultimately, I hope to contribute to a paradigm shift in how we understand and treat eating disorders, moving from symptom management to addressing root causes, thereby improving outcomes for individuals and reducing the broader societal impact.

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

I genuinely enjoy mentoring. Watching a student evolve from hesitant to confident or helping a postdoc land their next fellowship is incredibly rewarding. I also love the moment when data surprises you—when your assumptions are challenged, and you are forced to rethink. Those moments keep science dynamic and human.

At Genomic Press, we prioritize fostering research endeavours based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that you feel strongly devoted to?

There are two systemic issues in science that I am deeply committed to challenging: the lack of women in leadership, and the way our current funding and publishing structures erode space for long-term, creative thinking.

Despite progress, women continue to be significantly underrepresented in senior academic and research leadership roles. We see promising gender parity at the PhD level, but that pipeline narrows rapidly. The absence of women in decision-making positions on grant panels, editorial boards, and institute leadership shapes what questions get funded, who gets cited, and what voices are considered authoritative. It is not just an issue of fairness; it is a missed opportunity for more diverse, impactful science. I feel a strong responsibility to mentor and support emerging women scientists and to model leadership that is collaborative, transparent, and inclusive.

The second issue is structural: the current Australian research funding landscape is short-sighted and unsustainable. With major grant success rates hovering around 10%, researchers are locked into a relentless cycle of grant writing and publication-chasing that leaves little time for deep thinking or long-range vision. It is a system that penalises risk, creativity, and slowness—and rewards volume over substance. As Uta Frith argued in her article on Slow Science, "*Fast Science is bad for scientists and bad for science*." I could not agree more. We urgently need to rethink our metrics for success, not just the number of papers we publish but also how meaningful, reproducible, and forward-thinking our contributions are.

Ironically, the most innovative work I have done—the kind that opened up new directions in psychedelics research and eating disorder neuroscience—did not come from chasing high-impact metrics. It came from having space to explore an odd finding, a side project, or an unexpected conversation. These moments are increasingly rare in our current climate. If we want to foster genuine breakthroughs, we need to fund thinking time, not just outputs. In both gender equity and research culture, we need systemic change. This includes longer-term grants, improved recognition of mentoring and team science, and increased diversity in leadership. The problems we face, both scientific and societal, require big-picture thinking and sustained collaboration. That will not happen if we are all just racing to meet the next deadline.

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?

Travel and food are two of my greatest pleasures, and fortunately, my career often allows me to indulge in both. Academic life takes me to conferences and collaborations in some remarkable places, and I always try to carve out time to explore the local culture—especially through its food. Whether it is a hole-in-the-wall noodle shop in Tokyo or a leisurely dinner in a European wine region, I love how meals can anchor you in a place and create space for reflection and connection. In that sense, the boundaries between professional and personal life often blur, in the best possible way. If given a completely free weekend, I would probably plan a short

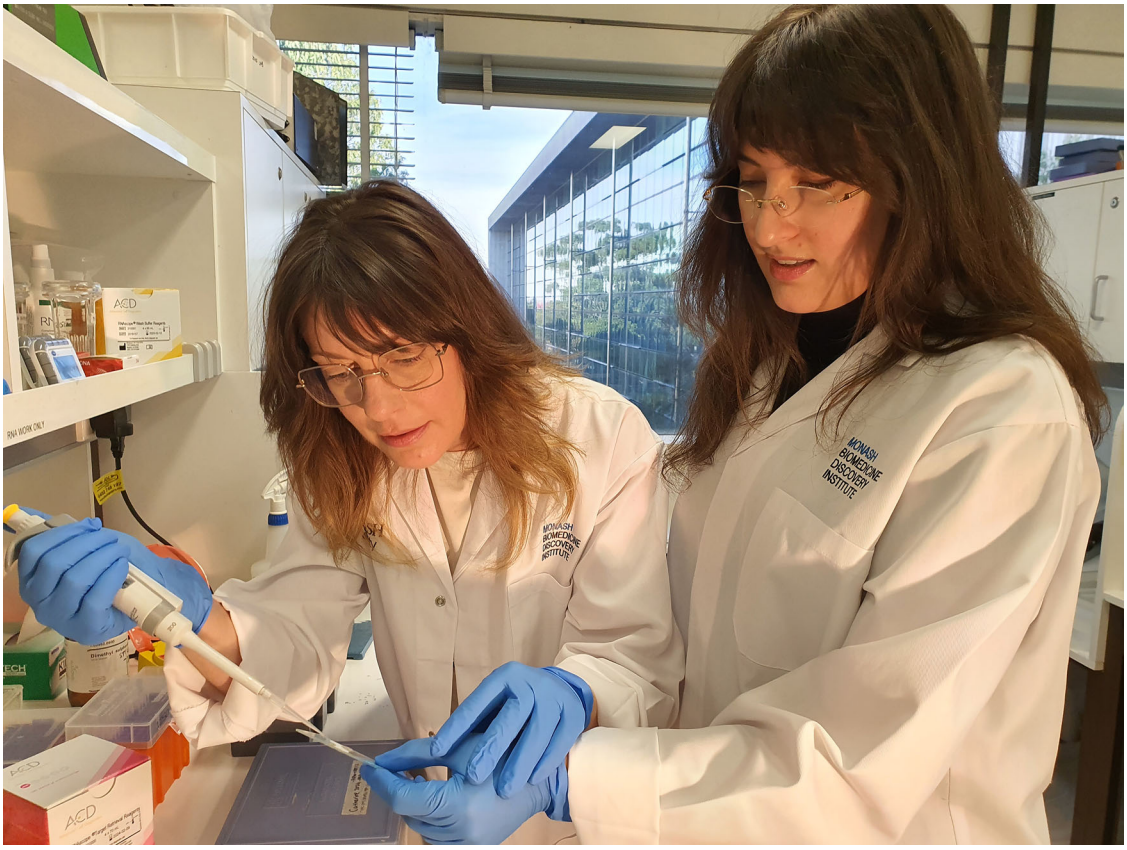

Figure 2. A/Prof Foldi in the lab with postdoc trainee Dr Kyna Conn.

getaway centred around local markets, natural landscapes, and a good glass of wine (or two).

Part 2: Claire J. Foldi – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
The "gift of the gab" – a natural ability to speak easily, confidently, and persuasively, especially when explaining ideas or engaging an audience.

Among your talents, which one(s) give(s) you a competitive edge?
Being unusually good at bringing diverse people together.

If you could change one thing about yourself, what would it be?
The need to rewrite everything three times before I believe it is coherent.

What is your current state of mind?
A precarious balance between focus and fatigue, managed mostly with to-do lists and caffeine.

What is your idea of perfect happiness?
A day where no one needs me urgently, and I can sit reading in silence without guilt.

What is your greatest fear?
That I will run out of time before I make enough sense of the world to say something worth remembering.

What is your greatest regret?
The years I spent waiting for permission instead of acting with confidence.

What are you most proud of?
When my students or trainees succeed in their pursuits.

What is your greatest extravagance?
High-end artisanal sea salt, freshly shucked oysters, and wine.

What is your most treasured possession?
My most treasured "possessions" are my cats, Edith and Anthony, but calling them possessions feels entirely inaccurate. They are companions, co-regulators, emotional anchors. They remind me to pause, to pay attention, and to feed someone other than myself on the hard days.

Where would you most like to live?
On an island, possibly somewhere in the South Pacific, where it is warm all year round.

What is the quality you most admire in people?
The ability to keep showing up after they have been disappointed.

[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 the trait you most dislike in people?
Entitlement without awareness. And the inability to laugh—especially at oneself. If we cannot find some absurdity in life, we are probably not looking hard enough.

What do you consider the most overrated virtue?
I would say solemnity. There is a misplaced belief that a serious demeanour must accompany important work. However, humour, lightness, and irreverence often make space for better ideas, more inclusive teams, and more resilient scientists.

What do you most value in your friends?
That they never ask me to be more optimistic than I actually am.

Who are your heroes in real life?
Richard Feynman and Haruki Murakami.

What aphorism or motto best encapsulates your life philosophy?
One motto I use in general life is the phrase "*say what you mean and mean what you say*," which serves as a compass for honest communication without hedging or hollow commitments. Professionally, I believe a perfect encapsulation of discovery science is the motto "*excellence through guesswork*."

Melbourne, Victoria, Australia
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Psychedelics

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PERSPECTIVE

Psychedelics and time: Exploring altered temporal perception and its implications for consciousness, neuroscience, and therapy

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Psychedelics including psilocybin, dimethyltryptamine, and lysergic acid diethylamide are known to disrupt the normal flow of time perception, for example, producing time dilation, compression, and loss of time. These temporal anomalies provide interesting clues about how the brain processes time, what consciousness is, and what produces the sense of self. This opinion article discusses the neural mechanisms of time perception altered by psychedelics by integrating emerging research findings in cognitive neuroscience and subjective effects. We suggest that the psychedelic-induced time warp can offer a new approach to studying brain correlates of the perception of the passage of time and conscious perception of time, and may have potential therapeutic value in psychiatric disorders in which altered perception of time is core, such as posttraumatic stress disorder, depression, and anxiety. Through examining these time changes, we discuss the potential of psychedelics in shaping transformative cognitive-affective states and their relevance for clinical applications.

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Keywords: Psychedelics, time perception, consciousness, temporal distortion, LSD, psilocybin

Introduction

Time perception has profound effects on human consciousness, influencing cognition, affect regulation and behavior. Most often experienced as one continuous experience, how we perceive past, present, and future affects our sense of self and everything we consider real (1). However, psychedelic substances like lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT) can profoundly alter this perception, leading to phenomena such as time dilation—where seconds feel like hours—or time compression—where hours pass in minutes (2). These distortions offer an insight into the brain as it processes time and disrupt the assumptions of traditional models of consciousness, reminding us how pliable something as fundamental as time—the primordial dimension that shapes our sense of self and our experience of the world—can be. Psychedelics can dissolve or reconfigure the boundaries between the self and the world, disrupting the continuous flow of time and allowing access to experiences of timelessness, transcendence, and unity with the universe. Understanding the influence of psychedelics on the experience of time is vital, not only for the development of theories of consciousness, but also for therapeutic purposes in mental health conditions such as depression, anxiety, posttraumatic stress disorder (PTSD), existential distress, grief and substance use disorders (3), where time perception and self-awareness are typically disconnected. Through dissolving the boundaries between past, present, and future, psychedelics provide a unique window to consciousness and a means of processing traumatic memories. This article examines the complex relations between psychedelics and time, with a focus on subjective effects, neural correlates and therapeutic applications of their ability to modulate temporal processing in ways that serve to unravel the mysteries of their effects in clinical and nonclinical settings.

Temporal distortions under psychedelic states

Psychedelic substances psilocybin, LSD, and DMT cause drastic changes in the perception of time, which users often describe in delirious metaphors. These distortions vary from the stretching and shrinking of time, to reaching a state of oblivion, in which there is no longer any appreciation of where time actually goes. One of the most frequently cited impacts of psychedelics is a perceived slowing of time (it feels like hours have passed when it's only been minutes). This change is commonly attributed to increased sensory processing, as psychedelics elevate neural oscillations in lower brain regions specializing in sensory input and emotional processing (4). Enhanced attention to sensory stimuli in a psychedelic state may interfere with time perception, as the brain attempts to process information at a higher rate.

At the other extreme, some people experience time distortion, with hours that feel like minutes. This could be due to intensive attentional or ego disintegration. Ego dissolution, a characteristic of high-dose psychedelic experiences, may loosen the individual's typical perceptual hold on time, such that time seems to accelerate. Less commonly considered, but relevant for understanding the psychedelic state, is time compression, which can be related to alterations in serotonin (5-HT) levels and the consequent effect on cortical activity, through the 5-HT_{2A} receptor (5).

A third, comparably remarkable feature is timelessness itself. Users frequently report a dissociation with the passing of time and a feeling of timelessness or eternity. This experience is often reported within profound mystical or transpersonal experiences, and is believed to be the product of changes in the default mode network (DMN) of the brain. The DMN is associated with self-referential thinking and perception of continuous time (6), and its suppression in psychedelic states may result in the dissolution of time as a boundary—so that past, present, and future are perceived as irrelevant or unified in a moment.

Because of the subjective nature of these temporal distortions, the experiences vary considerably depending on the type of drug, its dosage, and the individual's psychological set and setting. For example, psilocybin tends to be associated with experiences of timelessness, whereas LSD is more frequently related to profound time dilation (7). These distinctions observed between substances imply that differential pharmacological effects underlie the modifications to time perception, at least among psychedelics, demonstrating that the neural substrates that mediate these experiences are multifaceted. Overall, alterations in the

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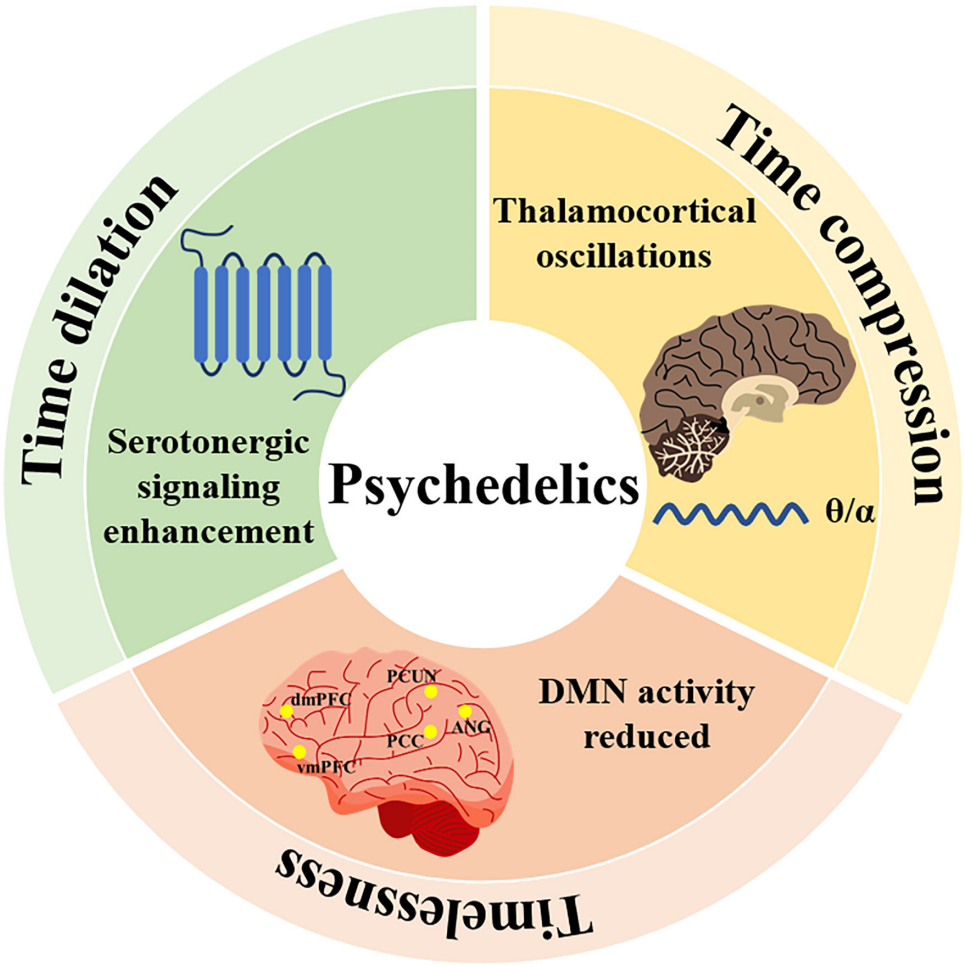

Figure 1. Neurobiological mechanisms of psychedelic-induced time perception alterations.

perception of time under psychedelics provide a novel perspective to study the brain mechanisms in temporal processing and open new perspectives for the study of the role of consciousness in influencing what we consider reality.

Neurobiological mechanisms of altered time perception

Time perception is a complex cognitive process that emerges from the integrated activity of distributed brain regions, neurotransmitters, and neural synchrony (Figure 1). The basal ganglia are implicated in interval timing on the scale of hundreds of milliseconds, where they function as a putative internal clock, generating temporal predictions based on sensory evidence. The prefrontal cortex encodes longer time spans and combines information for planning and making decisions, which is crucial for controlling dynamic time-based tasks. The cerebellum refines motor coordination and precise timing by integrating sensory input and motor output for the precise timing of events. By integrating interoception of internal body states with cognitive processes, the insula plays a role in modulating how emotions and somatic sensations shape our perception of time (8, 9).

Temporal processing is further regulated by major neurotransmitter systems. Dopamine, acting primarily through the basal ganglia, modulates shorter interval timing, and its dysregulation is linked to timing deficits. Serotonin, particularly via 5-HT_{2A} receptor activation, influences longer time scales and is the primary mediator of psychedelic-induced temporal distortions, interfacing emotional and sensory processing with subjective time experience. Glutamate, largely through N-Methyl-D-Aspartate (NMDA) receptor-mediated neurotransmission, supports the neural encoding and maintenance of precise temporal representations required for various cognitive tasks (10).

Precise time perception relies on temporal coordination of neural activity between distant brain areas, which is generally mediated by neural synchrony, that is, the simultaneous firing of neurons in diverse regions of the brain, via the tuning of neural oscillations such as theta (4–8 Hz) and gamma (30–100 Hz) rhythms. These rhythms are able to synchronize sensory, motor, and cognitive activities, and disturbances in this synchrony may result in a distorted perception of time (11). The system's inherent neuroplasticity makes it susceptible to modulation by factors such as attention, emotion, and psychoactive substances.

Psychedelics such as psilocybin, LSD, and DMT strongly affect the aforementioned neurobiological processes, resulting in disrupted time perception due to modulation of the brain's sensory, calm, and self-reference systems. A key brain network for the mediating role of these changes is the DMN, comprised of the medial prefrontal cortex, posterior cingulate cortex and the angular gyrus. Related to self-referential thinking and the brain's internal model of time, it is suppressed by psychedelics. This DMN suppression correlates strongly with subjective reports of time dissolution and the loss of linear time perception (6).

Psychedelics also modulate cortical oscillations in the theta and alpha range, where this integration of sensory information over time is important. Modulations of the amplitude and coherence of these oscillations can result in dissonance between sensory inputs and the brain's temporal predictions, thereby inducing perceptions of time dilation or compression. The thalamus, an important relay center for sensory information, is also crucial for temporal processing. Psychedelics modulate thalamic

activity, disrupting the synchronization of sensory inputs, which may result in time dilation, compression, or even timelessness (12).

The serotonergic system, particularly 5-HT_{2A} receptor activation, plays a central role in psychedelic modulation of time perception. Receptor activation enhances cortical excitability and increases the gain on sensory inputs, shifting precision toward bottom-up evidence and making temporal cues unusually salient; these network-level changes bias temporal processing and can appear as time dilation or compression. Membrane-receptor signaling can propagate via PLC-IP_3/Ca^{2+}, β-arrestin/ERK, and CaMKII pathways to influence mitochondrial fission and fusion and overall bioenergetics (e.g., DRP1 and OPA1), tune endoplasmic-reticulum Ca^{2+} handling and endoplasmic reticulum–mitochondria contact sites that shape integration windows, and reorganize the actin cytoskeleton through Rho GTPases, thereby modulating spine dynamics, synaptic integration, and neuronal excitability. By jointly tuning excitability, temporal integration, and oscillatory synchrony, these subcellular processes establish a mechanistic bridge between receptor pharmacology and the neural coding of duration and sequence. At the systems level, psychedelics also attenuate prefrontal top-down constraints on sensory cortices, disrupting hierarchical inference and thalamocortical gating, thereby weakening the brain's capacity to bind events into a coherent temporal narrative (13).

In summary, psychedelics produce neurobiological changes that perturb the brain's typical temporal processing. Through their influence on major brain areas and neurotransmitter systems, neural synchronies, and network connectivity, these substances underlie altered time perceptions which can manifest as the experience of time dilation/compression and also timelessness.

Therapeutic implications of psychedelic-induced temporal distortions

The shift in the perception of time that psychedelics produce could be incredibly valuable therapeutically, especially in mental health disorders where temporal perception is disturbed, like depression, anxiety, PTSD, or addiction. Psychedelics do, however, modulate passage-time experiences, triggering insights, emotional catharsis, and cognitive recontextualization, which are often crucial elements to healing (14).

A primary therapeutic application of psychedelics lies in the reprocessing of traumatic memories. Evidence from psychedelic-assisted psychotherapy trials for PTSD suggests that these substances enable individuals to revisit traumatic events from a detached, nonlinear perspective. Such dissociation facilitates the processing of past experiences with reduced emotional intensity, thereby supporting meaning-making and the integration of traumatic memories. In psychedelic-assisted psychotherapy for PTSD, such experiences of temporal decoupling—understood in part through suppression of the DMN and altered connectivity with limbic structures—have been described by patients as a significant factor in the change of symptoms.

Temporary time distortions induced by psychedelics could also act to promote other types of psychological healing by disrupting patterns of thought. These substances act as effective time distorters, allowing new angles on emotional trauma and cognitive structures to be processed, updated, and integrated in more insightful and forgiving ways. This can be especially constructive in a state of depression or anxiety, when people feel trapped in negative time loops or oppressed by impending hopelessness.

Additionally, psychedelics provide access to understanding mental illnesses involving distortions of the sense of time. By altering time perception quite radically, they present an opportunity to study the neural and cognitive processes of time disruption by their drug-induced modulation in conditions such as schizophrenia and PTSD. When taken under the supervision of trained therapists and in the right set and setting, psychedelics may do the work of rewiring neural circuits implicated in time processing and emotion regulation, and so lead to more adaptive time perceptions (13). The therapeutic potential and associated risks of this mechanism warrant systematic evaluation. A longitudinal study tracking individuals with treatment-resistant PTSD undergoing psychedelic-assisted therapy could be implemented, with objective measures of time perception (e.g., duration discrimination tasks) and neural activity functional Magnetic Resonance Imaging (fMRI) collected at baseline, immediately post-treatment, and during follow-up assessments.

However, these promising applications necessitate rigorous ethical consideration. Robust informed consent is paramount, ensuring patients understand the potential for profound alterations in consciousness, including distressing time distortions. Clinical protocols must include strategies to manage anxiety or confusion arising from these states. The risk of misuse demands administration only in controlled settings with professional oversight. Significant regulatory hurdles persist, as the classification of many psychedelics as Schedule I substances limits its research. Establishing clear safety monitoring guidelines and defining regulatory pathways for approval are essential for the responsible integration of psychedelics into therapeutics.

In conclusion, the manipulation of time perception by psychedelics offers a powerful, though not yet fully understood, therapeutic lever. It is through the manipulation of time perception that psychedelics enable the reprocessing of traumatic events, accelerating traumatic resolution and opening avenues to new paradigms of mental health disorders with time perception at their core. Their potential should be fully realized, but should be deployed in a responsible manner with careful ethical consideration.

Conclusion

In sum, psychedelics provide a novel lens to probe and illuminate the diverse aspects of time perception and consciousness. Through the alteration of timing, not only do these compounds further our knowledge significantly but, importantly, they also promise substantial therapeutic potential in a wide range of mental health conditions. By changing the brain's sense of time, the psychedelics provide a rare window into how time is processed in the brain, and how subjective time can be modified in conditions including depression, PTSD and schizophrenia. These time distortions from dissociation or involvement—such as time dilation, time compression, or timelessness—play a key role in psychotherapy as a way to give space for emotions, insights, and healing. As research progresses, elucidating the neurobiological substrates of these temporal shifts will be important in the search for effective treatments. Future work should focus on leveraging these effects in controlled clinical settings, employing rigorous designs that directly test the role of time perception in therapeutic outcomes. Such efforts will not only unlock the transformative therapeutic potential of these compounds but also expand the frontiers of our understanding of the human mind.

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Author contributions

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

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

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Author disclosures

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THOUGHT LEADERS INVITED REVIEW

Psilocybin's effects on obsessive-compulsive behaviors: A systematic review of preclinical and clinical evidence

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Psilocybin is a serotonergic psychedelic with growing evidence for efficacy in mood disorders, and its therapeutic potential in obsessive—compulsive disorder (OCD) and related conditions is increasingly recognised but remains understudied. We systematically evaluated clinical and preclinical evidence on psilocybin's effects on obsessive and compulsive behaviours with attention to translational relevance. A systematic search identified 13 eligible studies (4 clinical trials and 9 preclinical investigations examining psilocybin or psilocin on obsessive—compulsive symptoms or behaviours), and reporting followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In clinical studies, single doses of psilocybin led to rapid reductions in obsessive-compulsive symptoms, including in patients with OCD and body dysmorphic disorder. In wild-type mice, psilocybin acutely decreased marble-burying behaviour, although this effect was transient and not observed beyond the first day after administration. In contrast, in SAPAP3 knockout mice—a validated genetic model of compulsive behaviour—a single administration of psilocybin produced robust, enduring reductions in excessive grooming, and these lasting anti-compulsive effects were replicated across independent laboratories and doses. Additionally, chronic hallucinogenic doses of psilocybin did not improve anxiety-like or compulsive-like behaviour in SAPAP3 knockout mice; however, a separate study in Long—Evans rats found that chronic sub-hallucinogenic psilocybin reduced self-grooming and enhanced expression of synaptic markers in the paraventricular thalamus. Together, the evidence suggests that psilocybin transiently reduces obsessive—compulsive symptoms in clinical populations and produces lasting anti-compulsive effects in validated animal models. Future clinical studies should include larger placebo-controlled trials and incorporate neuroimaging to assess psilocybin's impact on fronto-striatal circuitry implicated in OCD pathophysiology.

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Keywords: Psilocybin, obsessive, compulsive, behaviors, systematic review

Introduction

Psilocybin, the psychoactive compound found in some species of fungi, has been long known for its psychedelic properties. Acute ingestion induces physiological and psychological effects, including a transient increase in blood pressure, feelings of euphoria, perceptual disturbances, and altered states of consciousness (1). While the therapeutic applications of psychedelic substances is an emergent field in modern Western medicine, the use of naturally occurring psychedelics for psychological and spiritual benefit has been commonplace in many traditional medicine frameworks for millennia (2).

At present, the strongest empirical data indicating the therapeutic potential of psilocybin has been found in major depressive disorder (MDD). For MDD, there is compelling evidence from double-blind randomized control trials (RCTs) that points to enduring benefits to mood, following even a single dose of psilocybin in a clinical setting [see review of RCTs in Wang *et al*. (2023) (3)]. Encouragingly, positive results have even been found in patients with treatment-resistant depression (4).

Upon human ingestion, psilocybin is rapidly metabolized to psilocin, which shares a similar chemical structure to endogenous serotonin and is a potent serotonin 5-HT_{2A} receptor agonist (5). While 5-HT_{2A} receptor agonism has been found to underpin the acute psychoactive properties of psilocybin, as well as neuroplastic processes (6), other studies have found 5-HT_{2A}-independent neuroplasticity (7). The activation of neurotrophic pathways and the promotion of cellular and synaptic plasticity may imply some common therapeutic mechanisms between psilocybin and other known antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or ketamine (8).

While there is an established base of evidence supporting the utility of psilocybin in the management of mood disturbances, its therapeutic potential in the treatment of obsessive-compulsive disorders (OCDs) is only beginning to be understood. Arguably, the most well-characterized illness within the obsessive-compulsive and related disorders (OCRD) spectrum is OCD, which affects as many as 2%–3% of the general population throughout their lifetime (9, 10). This illness is characterized by unwanted and distressing thoughts, images, or urges (obsessions), and/or highly repetitive/ritualistic behaviors, such as excessive washing or checking (compulsions) (11). Standard treatment consists of psychological therapy with adjunct pharmacotherapy (usually a high-dose SSRI); however, many patients report incomplete symptom remission (12, 13).

OCD is highly polygenic and environmentally sensitive, making the development and investigation of new pharmacotherapies a challenging endeavor (14). However, convergent lines of evidence suggest dysregulation of the glutamatergic and serotonergic systems in OCD, in both clinical studies and in preclinical models (15–18). Serotonergic genetic candidates include polymorphisms of 5-HT transporter and 5-HT_{2A} receptors (18). Interestingly, while some serotonergic agents such as SSRIs can be effective in treating compulsive behaviors, serotonergic 5-$HT_{1A/1B}$ and 5-$HT_{1A/1D}$ antagonists, such as RU-24969 and sumatriptan, have been found to exacerbate obsessive compulsive–like symptoms in both humans and rodents (19, 20).

Very recently, new evidence has begun to emerge pointing to the therapeutic potential of psilocybin in the treatment of OCRD-spectrum disorders. However, as it will be discussed in detail below, the field is lacking in well-powered high-quality clinical studies, and few attempts

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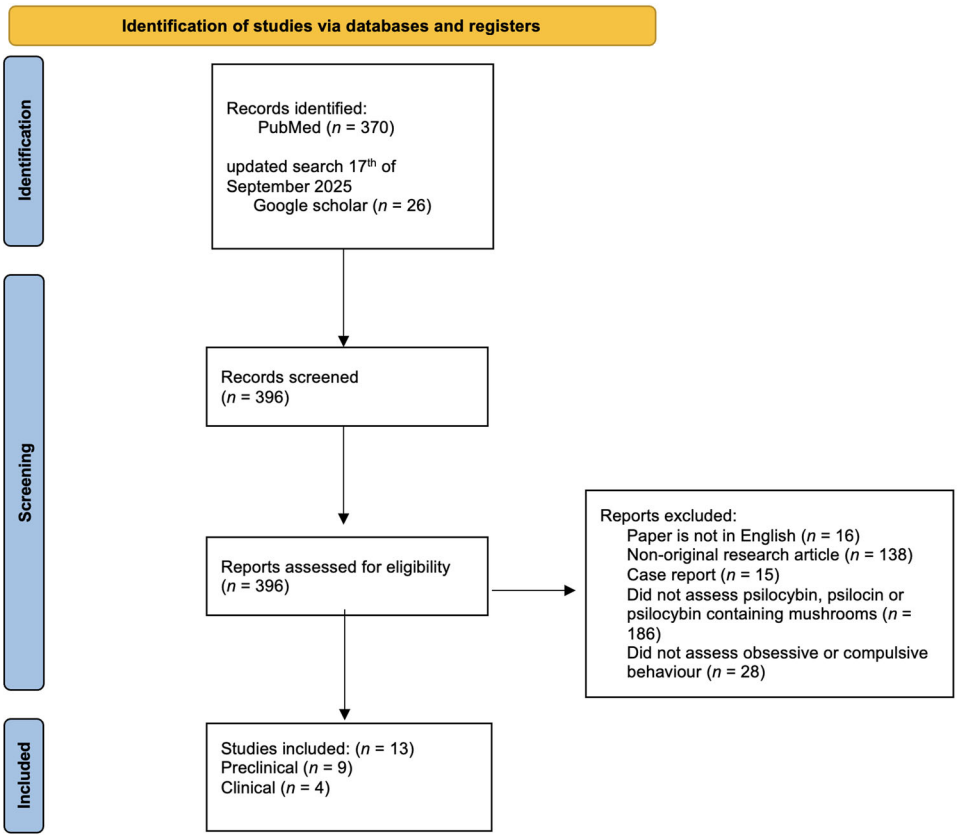

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (21) for study selection.

have been made to synthesize a consensus of available data. There is a greater weight of evidence in rodent studies, and indeed we have previously asserted that psilocybin could be considered as a lead candidate molecule in preclinical studies of neuropsychiatric disorders, including OCD (22). Notably, there have been recent reports of the efficacy of psilocybin in the most well-characterized animal model of OCD (23–26).

Although previous reviews have examined the therapeutic potential of psilocybin for OCD (27–30), none was conducted systematically. Our review addresses this gap and extends the discussion to psilocybin's therapeutic potential across the full OCRD spectrum.

Here, we will systematically review the available evidence on psilocybin's enduring therapeutic effects on obsessive-compulsive behaviors. By synthesizing preclinical and clinical lines of evidence, we aim to present a current scientific consensus on the utility of psilocybin to treat OCRD spectrum disorders, including OCD, and provide a clear direction for future research.

Results

The search string resulted in the identification of 370 articles on PubMed. An additional updated search was conducted on September 17, which identified another 26 studies. Applying the exclusion criteria resulted in the exclusion of 383 articles, leaving 13 articles to be included in the review (Figure 1 and Figure 2; Table 1). Of these articles, 9 where preclinical and 4 were conducted in clinical populations.

Discussion

Therapeutic efficacy across studies

Psilocybin administration in clinical populations When synthesizing the papers included in this review, a consistent theme emerges: psilocybin is capable of reducing obsessive and compulsive symptoms in clinical and compulsive-like behavior in preclinical studies. For instance, Moreno *et al*. (2006) (31) found that at a range of doses (25–300 μg /kg, oral), psilocybin significantly decreased obsessive and compulsive symptoms between 4 and 24 h compared to baseline in patients with treatment-resistant OCD. The reduction in obsessive and compulsive symptoms was comparable. In another pilot study, Schneier *et al*. (2024) (32) found that a single dose of 25 mg of psilocybin (oral) significantly decreased obsessive and compulsive symptoms related to body dysmorphic disorder at 1, 2, 3, 6, and 12 weeks after administration compared to baseline, with a large effect size. This study was conducted in patients with body dysmorphic disorder (BDD) which is classified by the American Psychiatric Association within the cluster OCRD recognizing its similarity to other disorders with repetitive and ritualistic elements (11). In addition to BDD, this cluster of disorders includes OCD, trichotillomania (hair pulling disorder), hoarding disorder, and dematillomania (skin pricking disorder). It has been argued that this clustering of disorders reflects a common underlying construct of maladaptive harm avoidance juxtaposed with the subjective feeling of "sensory incompleteness" (33).

BDD is defined by distressing preoccupation such as mirror checking and gazing, disproportionate grooming, modification or camouflaging of appearance, and mentally comparing appearance to that of others (11). Thus, BDD is related to OCD both behaviorally and neurobiologically and is often comorbid (34) and has been referred to as a disorder of "obsession with perfection" (35). Thus, psilocybin's reduction in obsessions and compulsions related to BDD, highlights psilocybin's transtherapeutic potential for disorders across the OCRD spectrum.

Furthermore, Buot *et al*. (2023) (36) found that participants who had consumed psilocybin-containing mushrooms had a significant reduction in their OCD symptomatology. Although in their subsequent analysis they combined the results of participants who had consumed lysergic acid diethylamide (LSD) and psilocybin-containing mushrooms, they found that approximately 30% of users found a persistence in effects for more

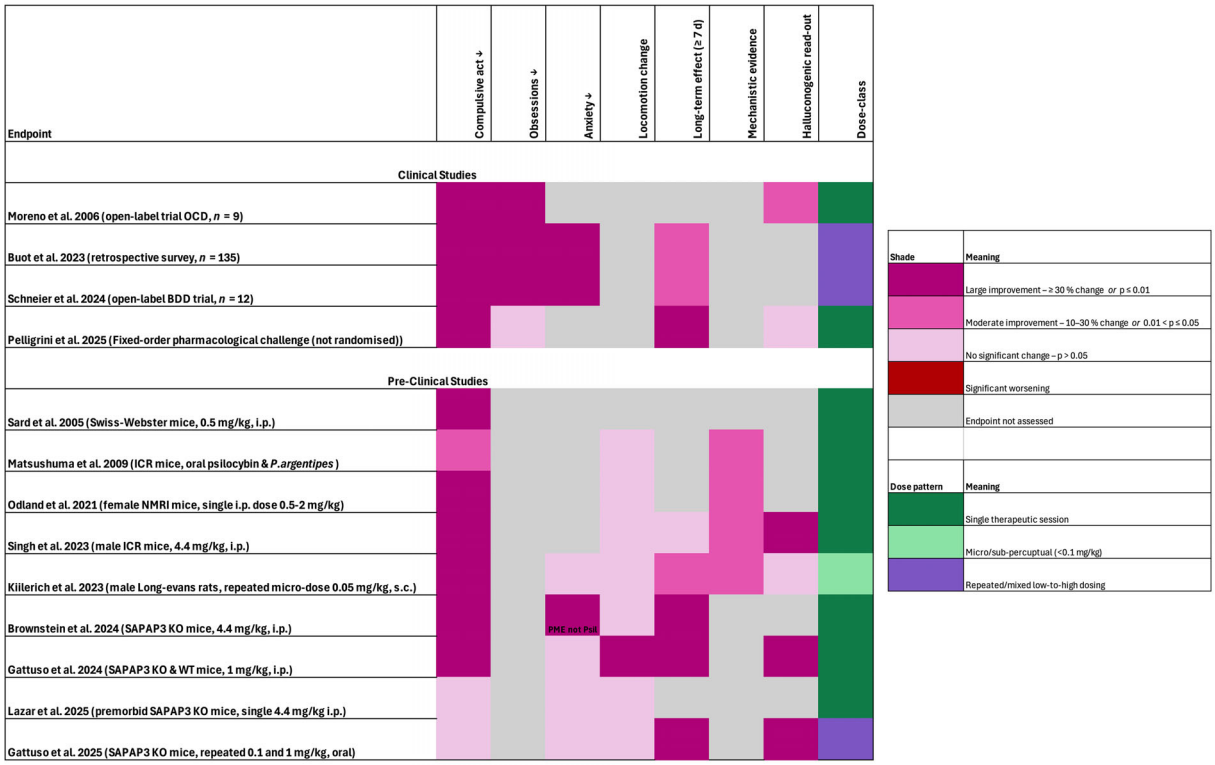

Figure 2. Cross-study heat map of psilocybin's behavioral and mechanistic effects in obsessive-compulsive related animal models and patients. Rows list the 13 primary studies reviewed (4 clinical at top, 9 preclinical beneath, ordered chronologically). Columns display seven endpoints that recur across ≥ 3 papers. It is important to note that effect magnitudes vary widely across species and paradigms.

Table 1. A summary of studies included in the systematic review

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Clinical Papers				
Moreno *et al.* (2006) (31) **Open-label trial**	Psilocybin doses were 25 [very low dose (VLD)], 100 [low dose (LD)], 200 [medium dose (MD)], and 300 [high dose (HD)] μg/kg of body weight (orally ingested). LD, MD, and HD were assigned in that order and the VLD was inserted randomly and in a double-blind fashion at any time after the first dose (LD). Testing days were separated by a week. All 9 subjects received LD, 7 of them also received the VLD and MD and 6 of them received all 4 doses. There was no placebo control group.	$n = 9$ subjects (7 male, 2 female). Age (mean ± SD) = 40.9 ± 13.2 Subjects were required to have at least one "treatment failure" defined as a lack of significant improvement after an adequate treatment course with a serotonin reuptake inhibitor for at least 12 weeks. Subjects were required to have well tolerated at least one indole-based psychedelic drug. Subjects were required to abstain from use of antidepressants for at least 2 weeks (6 weeks for fluoxetine) before testing.	The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and a Visual Analogue Scale (VAS) for overall obsessive-compulsive symptom severity was administered immediately before psilocybin ingestion (baseline) and 4, 8, and 24 h postingestion. The hallucinogen rating scale (HRS) was administered at 8 h postingestion.	Marked decreases in OCD symptoms (23% – 100% reduction in YBOCS score) was observed in all subjects during 1 or more sessions. There was no significant effect of dose ($p = 0.261$) or dose x time interaction ($p = 0.515$) for YBOCS scores. When all doses were combined, post ingestion YBOCS scores was significantly less than baseline ($p = 0.028$) (time points range from 4 to 24 h) A similar pattern of results was observed for the VAS. The HRS intensity was dose-dependent ($p = 0.017$), however, there was no association between HRS intensity and symptom severity.
Buot *et al.* (2023) (36) **Retrospective online survey**	Participants needed to have at least one experience taking psilocybin-containing mushrooms.	Participants were included if they had a diagnosis of OCD performed by a health professional, or an OCI-R score greater than 18 or both. 135 participants had reported consuming psilocybin-containing mushrooms.	Changes in OCD symptoms were assessed using 6 items: negative emotions, obsessions, compulsions/rituals, anxiety, acceptance of condition, and avoidance of possible anxiogenic situations. Each item was scored by moving a cursor on a 100-point scale starting at midpoint (0: no change) and ranging from −100 (Worsening) to +100 (Improvement).	Individuals who had consumed psilocybin-containing mushrooms had significantly improved OCD symptomatology ($p < 0.001$).

(*continued*)

Table 1—*Continued*

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Schneier *et al*. (2024) (32) **Open-label trial**	25 mg dose (oral) of psilocybin was administered to participants. There was no control group.	$n = 12$ adults (8 women and 4 men) Age (mean ± SD) = 34.31 ± 8.86 Diagnosed with nondelusional body dysmorphic disorder (BDD) ≥6 months. Required moderate severity (BDD-Y-BOCS ≥24, Clinical Global Impression Severity Scale or CGI ≥4) and nonresponse to at least one adequate trial of SRI, SNRI, or clomipramine at dose equivalent to ≥20 mg/day fluoxetine for ≥2 months. Exclusion criteria included severe depression (Hamilton Rating Scale for Depression score > 20), current suicidality or a suicide attempt within the past year, bipolar disorder, psychotic disorders, active substance use disorder within the past 3 months, use of investigational medication within 3 months, depot antipsychotic within 6 months, or serotonergic medication within 2 weeks (6 weeks for fluoxetine). All participants completed all study assessments through 12 weeks.	The primary outcome was BDD symptom severity, measured using the clinician-rated BDD-Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (range: 0–48; higher scores = greater severity). Assessments occurred at baseline (day −1), day 0, day 1, and weeks 1, 2, 3, 6, 9, and 12 postdosing. Response was defined as a ≥30% reduction in total score; remission as a score ≤16.	BDD-YBOCS scores decreased significantly over 12 weeks ($F_{1.92, 21.13} = 13.08$, $p < 0.001$, $\eta^2 = 0.54$), with a mean reduction of 13.33 points from baseline at week 12. Scores were significantly lower than baseline at all time points except week 9 (trend-level, $p = 0.059$). At week 12, 7 participants (58.3%) met response criteria (≥30% BDD-YBOCS reduction or CGI score of 1–2); 4 of these also met remission criteria (BDD-YBOCS ≤16).
Pellegrini *et al*. (2025) (37) **Fixed-order double-dose pharmacological challenge (not randomized)**	Participants received two single doses of oral psilocybin administered in a fixed order and separated by at least 4 weeks. The first dose was 1 mg/kg oral psilocybin which served as a very low control dose. The second dose was the active treatment (10 mg/kg, oral), which was administered at least 4 weeks after the first dose.	$n = 19$ adult participants 1 participant had to leave the study for personal reasons. The mean age of participants was 38 years and $n = 13$ were male and $n = 6$ were female. Participants must have had suffered from OCD for at least 12 months and were of moderate severity. 58% of participants were using medications (SSRIs). 14 participants were psychedelic naïve. Key exclusion criteria included a current or previous diagnosis of psychotic disorder, bipolar disorder or mania, having a first-degree relative with a diagnosed psychotic disorder, a history of serious suicide attempts (requiring hospitalization), or borderline personality disorder. Participants also needed to have stable physical health.	The primary clinical outcome was the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Y-BOCS was conducted at several time points: 1 day before each dose (baseline 1 and 2), and then 1 week, 2 weeks, and 4 weeks following each dose. The assessor who was blinded to drug treatment.	Y-BOCS scores significantly decreased over time ($p < 0.0001$), with the largest reduction at 1-week post-10 mg ($\beta = -3.63$, $d = 1.12$, $p < 0.0001$). Dose effect was significant at 1 week ($\beta = -4.49$, $d = 0.82$, $p = 0.002$), trend level at 2 weeks ($\beta = -3.34$, $d = 0.45$, $p = 0.06$), and nonsignificant by 4 weeks. Compulsions improved more than obsessions at 1 week ($\beta = -2.44$, $d = 0.74$, $p = 0.003$ vs. $\beta = -1.78$, $d = 0.50$, $p = 0.06$).

(*continued*)

than 3 months. Interestingly, users who reported consuming psilocybin-containing mushrooms (or LSD) on more than one occasion had a stronger improvement in OCD symptoms [47% ($n = 42$) reported an intake frequency of at most three times a year, 14% ($n = 13$) reported once a month and 16% ($n = 14$) at least once a week].

Finally, the most recent clinical study is by Pellegrini *et al*. (2025) enrolled 19 adults with moderate-to-severe OCD who received two single oral doses of psilocybin (1 mg followed by 10 mg, separated by at least 4 weeks) in a fixed-order design. Psilocybin produced a rapid reduction in OCD symptoms, with the 10 mg dose leading to the strongest improvement, particularly in compulsive symptoms. However, these effects were transient, diminishing after 1 week and no longer evident by 4 weeks.

Methodological limitations of included clinical studies Although these preliminary findings are encouraging, there are several methodological limitations, which warrants cautious consideration when interpreting these results. First, a major limitation of Moreno *et al*. (2006) (31) was the lack of a placebo control group; thus, it is impossible to delineate how much of the reduction in obsessive and compulsive symptoms was due to true treatment effects. Furthermore, this study contained a very small samples size of only 9 patients and had limited longitudinal data (the

Table 1—*Continued*

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Preclinical Papers				
Sard *et al.* (2005) (38) **Preclinical medicinal chemistry study (SAR) with in vivo testing in a behavioral mouse OCD model.**	All drugs were dissolved in saline (0.9% NaCl) with 1 mg/mL ascorbic acid. Paired testing: each trial involved two mice, one control and one experimental (mice were placed individually in plexiglass boxes). Injection protocol: • Control mice: 10 mg/kg of ascorbic acid in saline, i.p. • Experimental: test compound (psilocin, psilocybin, or analog) dissolved in saline + ascorbic acid, also via i.p. injection. • After 5 min both mice were injected with 0.1 mL of 0.4 mg/mL serotonin, delivered s.c. into the rostral back. Doses of test compound injected: • Psilocin: 0.5 mg/kg • Psilocybin: 0.5 mg/kg • Analogs: 5 mg/kg Analog compounds: *Compound 3*: 1-methylpsilocin *Compound 4:* 1-methylpsilocybin *Compound 5:* 1-butylpsilocin *Compound 9:* 4-fluoro-N,N-dimethyltryptamine	Male Swiss–Webster mice, 4–6 weeks old. $n = 5$–12 per group. Psilocin $n = 7$ Psilocybin $n = 5$ *Compound 3:* $n = 12$ *Compound 4:* $n = 8$ *Compound 5:* $n = 5$ *Compound 9:* $n = 5$	Cumulative hind paw scratches were recorded every 5 min for 30 min post 5-HT injection. Hind paw scratching was an animal behavior relevant to pruritic psychological disorders such as OCD and excursion disorder.	Psilocin (0.5 mg/kg): ≈ 300 scratches at 15 min vs. control (≈ 400 scratches). **Psilocybin (0.5 mg/kg): ≈ 50 scratches at 15 min; vs. control (≈ 800 scratches). **Compound 3* (5 mg/kg): ≈ 180 scratches at 15 min vs. control (≈ 400 scratches). ***Compound 4* (5 mg/kg): ≈ 100 scratches at 15 min; strong inhibition vs. control (∼900 scratches). *Compound 5* (5 mg/kg): ≈420 scratches at 15 min; vs. control (≈500 scratches). ***Compound 9* (5 mg/kg): ≈100 scratches at 15 min vs. Control (≈900 scratches). Statistical significance: $^{*}p < 0.05$, $^{**}p < 0.01$.
Matsushima *et al.* (2009) (39) **Preclinical behavioral mouse model study (marble-burying)**	Fluvoxamine, Psilocybin, Psilocin, and *Phlebotomus argentipes* were tested for effects on marble-burying behavior in mice. • Fluvoxamine: i.p. injection (0.1 mL/10 g body weight) 30 min before test. • *P. argentipes*, Psilocybin, and Psilocin: oral administration (0.1 mL/10 g body weight) Concentration ranges from 0.05–2 g/kg for *P. argentipes* and 0.025–1.5 g/kg for psilocybin.	Five-week-old male ICR (Charles River Laboratories Japan) male mice. *P. argentipes* ($n = 10$) Psilocybin ($n = 10$)	Marble-Burying Test • Measured number of marbles buried at least two-thirds deep within 30 min. The test was conducted 30 min after drug administration. Locomotor Activity Test measured average total movement over 30 min.	*P. argentipes* at 0.05–2 g/kg showed a trend toward inhibiting marble-burying behavior while 0.1–1 g/kg significantly reduced the number of buried marbles ($p < 0.05$) No significant effect on locomotor activity at any dose ($p > 0.05$) Inverted bell curve in dose-response relationship (initial reduction in marble-burying, but increase at the highest dose) Reduction in marble-burying was not related to hallucinogenic-like effects or 5-HT_{2A} receptor activation *P. argentipes* was comparable to fluvoxamine, which also inhibited marble-burying without affecting locomotion. HPLC analysis showed *P. argentipes* contained 0.024% psilocybin and 0.0008% psilocin Psilocybin at 1.5 mg/kg significantly reduced marble-burying behavior, but *P. argentipes* was more effective at lower doses Findings suggest anti-OCD effects of *P. argentipes* are distinct from psilocybin alone, likely due to entourage effects.

(*continued*)

Table 1—*Continued*

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Odland *et al*. (2021) (40) **Preclinical behavioral mouse model study (marble-burying)**	**Psilocybin:** 0.5, 1.0, or 2.0 mg/kg, i.p. **DOI:** 1.0 mg/kg **Citalopram:** 2.5 mg/kg Antagonists: • **M100907** (5-HT_{2A} antagonist): 0.1 mg/kg • **SB24084** (5-HT_{2C} antagonist): 3.6 mg/kg Psilocybin was administered 15 min before testing; the other compounds were administered 30 min prior.	**Strain:** Female NMRI mice **Age:** 17–26 weeks Total $n = 100$ mice Group size per test: Typically, $n = 9$–10 per group	**Marble-Burying (MB) Test:** Used to assess compulsive-like/repetitive digging behavior. Measured marbles buried at 10, 20, and 30 min. **Locomotor Activity Test:** Assessed whether changes in digging were due to sedation or motor changes. Distance traveled recorded for 45 min.	Psilocybin (1.0 and 2.0 mg/kg) significantly reduced marble burying at 30 min ($p = 0.002$) and all doses (0.5, 1.0, 2.0 mg/kg) reduced digging in the first 10 min ($p \leq 0.001$). Psilocybin did not affect locomotor activity ($p = 0.616$), indicating a specific anti-compulsive effect. DOI reduced digging ($p < 0.001$), an effect blocked by the 5-HT_{2A} antagonist M100907 ($p < 0.001$), but not by the 5-HT_{2C} antagonist SB242084 ($p = 0.312$). Citalopram reduced digging ($p = 0.005$), and this effect was blocked by SB242084 ($p = 0.018$) but not by M100907 ($p = 0.082$). Psilocybin's effect on digging was not blocked by either M100907 ($p = 0.188$) or SB242084 ($p = 0.857$), suggesting a 5-HT2A/2C-independent mechanism.
Singh *et al*. (2023) (41) **Preclinical behavioral mouse model study (marble-burying)**	Mice were administered one or a combination of vehicle, psilocybin (4.4 mg/kg), escitalopram (5.00 mg/kg), 8-hydroxy-dipropylamino-tetralin hydrobromide (8-OH-DPAT; 2.00 mg/kg), M100907 (also known as volinanserin; 2.00 mg/kg), buspirone (5.00 mg/kg) or WAY100635 (2.00 mg/kg) dissolved in saline or DMSO and administered via intraperitoneal injection in a standard volume of 300 μL. The control group received an i.p. injection of vehicle (0.9% saline). **Administered 30 min prior to behavioral testing** (for the marble-burying test).	**Strain**: Male ICR (CD-1) outbred mice. **Animal Age:** Not provided. $n = 6$–17 per group **Baseline behavioral analysis:** Mice underwent a pretest of the MBT (without any drug) at least 1 week prior to the main experiment to identify those that reliably buried more than 15 marbles (the inclusion criterion).	**Marble burying test:** Twenty glass marbles were placed in a cage with approximately 4.5 cm of sawdust. Mice were placed in the cage for 30 min. A marble was considered "buried" if two-thirds or more of it was covered. **Open-field test:** Began immediately after MBT. A 30-min session in a 50 × 50 × 40 cm arena. Locomotion was recorded (total distance traveled, center vs. periphery time) **Head twitch response:** Measured with a magnetometer approach for 20 min postinjection.	**Marble burying:** • Psilocybin 4.4 mg/kg acutely decreased marble burying compared to vehicle. • This anti–marble-burying effect did not persist to day 7. • Bolus injection of the entire dose was required. Spacing the same total dose over 3 h did not reduce marble burying. • Neither 5-HT_{2A} (M100907) nor 5-HT_{1A} receptor (WAY100635) antagonism prevented psilocybin's effect. • 8-OH-DPAT (a 5-HT_{1A} agonist) and psilocybin each reduce marble-burying behavior in mice and show an additive effect when given together. **Open-field test:** • No reduction in locomotion was observed in psilocybin-treated mice compared to vehicle. • Hence, a decrease in marble burying was not attributable to impaired mobility. **Head twitch response:** • Psilocybin elicited a significant increase in head twitch behavior. • Coadministration of buspirone (a 5-HT_{1A} partial agonist) abolished that psilocybin-induced head twitch increase. • Blocking head twitch response did not diminish psilocybin's anti–marble-burying effect. **Mechanistic Findings:** Overall, psilocybin's acute reduction of marble burying occurs through yet-unidentified receptors/targets, distinct from the classical 5-HT_{2A} and 5-HT_{1A} pathways that often underlie its psychedelic effects.

(*continued*)

Table 1—*Continued*

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Kiilerich *et al*. (2023) (42) **Preclinical behavioral rat model study (self-grooming)**	**Occupancy study:** Doses of psilocybin used were 0.05, 0.20 and 1.0 mg/kg (s.c.) to establish 5-HT_{2A} receptor occupancy and detect overt psychedelic responses (e.g., wet-back shakes). **Chosen Microdose:** 0.05 mg/kg s.c., repeated every second day for 3 weeks. This dose was chosen because it did not induce wet-back shakes.	**Male Long-Evans rats.** Sample size varied by behavior, but the lowest sample size was $n = 8$ per group. **Animal Age:** Not provided.	**Occupancy/Wet-Back Shake:** Single subcutaneous injections (various psilocybin doses). PET scans with 10 MBq [^{18}F]MHMZ and subsequent wet-back shake counts. **Open-Field (OF) and elevated plus maze:** The rats were first given a short open-field test (15 min). Then they were placed on a 15-min elevated plus maze. **Acoustic startle reflex and open-field behavior:** Rats' startle reflexes are pre-assessed on separate days. On the final test day, they spend 40 min in the open-field, immediately followed by 37 min of PPI (total 80 min), with no injections given that day. **Sucrose preference test:** Five trials, about 1 week apart. First two trials are baseline, next two during psilocybin or saline regimen, the final trial was 2 days after the last injection. Each trial lasts 2 days.	**Low-dose psilocybin does not induce anxiety in a familiar environment:** • Rats received 0.05 mg/kg psilocybin every other day for 24 days. • No changes in locomotion, time in center, or center entries. • Rearing behavior was also unchanged. **Repeated low doses of psilocybin reduces compulsive behavior in a familiar environment:** • Psilocybin microdosing (0.05 mg/kg) reduced self-grooming frequency by 14% compared to controls ($p = 0.016$) in a familiar open field. **Repeated low doses of psilocybin does not induce schizophrenic-like behaviors:** • Low-dose psilocybin had no effect on startle reflex or %PPI ($p > 0.05$). • Startle habituation was present in controls ($p = 0.007$) but blunted in psilocybin group ($p > 0.05$). **Sucrose preference** • Control rats showed reduced sucrose preference during treatment (50% ± 27%, $p = 0.03$). • Psilocybin-treated rats maintained or increased sucrose preference (92.7% ± 5.2%), showing resistance to anhedonia. Repeated low-dose psilocybin did not affect anxiety or exploration in novel environments (open field or elevated plus maze). However, it reduced self-grooming by 48%. No behavioral desensitization observed: rats repeatedly given low-dose psilocybin still showed a full wet-back shake response when later given a high (1 mg/kg) psilocybin dose. No changes in 5-HT_{2A} or 5-HT_{2C} receptor levels in the prefrontal cortex, striatum, or choroid plexus. Psilocybin increased 5-HT_7 receptor expression and increased levels of synaptic vesicle protein 2A in the paraventricular nucleus of the thalamus ($p = 0.02$ and $p < 0.0001$).

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last time point was only 24 h post-administration). Additionally, this patient population was resistant to at least one prior treatment and, therefore, these results may not be able to be extrapolated to clinical populations who respond to frontline pharmacotherapy. Similarly, the study by Schneier *et al*. (2024) (32) also featured a very low sample size of only 12 patients; however, they did report large effect sizes (which is independent of sample size). Although, due to the absence of a placebo control group, how much of this effect size is due to placebo and expectancy effects cannot be determined. Finally, while Buot *et al*. (2023) (36) was a retrospective online survey, and therefore not limited by low statistical power, there are numerous other limitations associated with this study design. In a similar fashion to Moreno *et al*. (2006) (31) and Schneier *et al*. (2024) (32), a lack of a placebo control group limits interpretability of the results. Web-based surveys are also subject to bias in participant selection. For instance, participants who had more favorable experiences with psilocybin may have been more likely to complete the survey. Additionally, precise dose and duration of effects cannot be determined in this experimental design.

Although the results from Pellegrini *et al*. (2025) (37) are timely and help propel the knowledge base forward, the results should be interpreted with caution due to several important limitations. The study included only 19 participants, restricting statistical power and generalizability. The fixed-order design (1 mg always preceding 10 mg) introduced potential biases, and despite a 4-week washout, carry-over effects cannot be excluded. Blinding was imperfect, as nearly all participants correctly identified the 10 mg dose, raising the possibility of expectancy-driven influences. The use of 1 mg psilocybin as an active control also posed challenges, as it is unclear whether this lower dose was clinically inert and

Table 1—*Continued*

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Brownstien *et al.* (2024) (23) **Preclinical genetic knockout mouse model**	Psilocybin was administered only once, at a dose of 4.4 mg/kg i.p. 10.15 mg of psychedelic mushroom extract (PME) per 30 g mouse was administered i.p. This dose ensured each mouse received approximately 4.4 mg/kg of psilocybin. The control treatment was saline. 21 days posttreatment, mice whose total self-grooming behavior was decreased by 10% or more did not receive any further treatment and were reassessed 28 and 42 days after treatment. Mice in the saline group whose grooming had worsened by more than 10% but had no skin lesions were assigned to receive either psilocybin or PME. The grooming behavior of these mice was assessed 7 and 21 days after the second injection.	**Baseline behavioral analysis** SAPAP3 KO ($n = 10$) and WT (exact strain not specified) mice ($n = 10$). **Posttreatment** Male and Female SAPAP3 KO mice (28 males, 22 females). **First injection:** Saline ($n = 18$), PME ($n = 16$) Psilocybin ($n = 16$). **Second injection:** PME ($n = 13$) and psilocybin ($n = 12$). Mice were 6–7 months old. KO mice with skin lesions were removed from the study.	**Total self-grooming duration** (measured 2, 12, and 21 days posttreatment) **Head/body twitch** (measured 2, 12, and 21 days posttreatment) **Marble-burying test** (3 days posttreatment) **Open-field test** (3 days posttreatment) **Elevated plus maze** (5 days posttreatment)	**Baseline behavioral results** Before treatment, SAPAP3 KO mice exhibited increased grooming and head/body twitches compared to WT mice. SAPAP3 KO did not display significantly different distance traveled in the open-field test. However, they did spend significantly less time in the center ($p < 0.0001$). KO mice, spent significantly less time on the open arm of the elevated plus maze ($p < 0.0001$) and buried significantly less marbles in the marble-burying test ($p < 0.0001$) **Post-treatment results** Psilocybin and PME significantly reduced grooming duration at 12 and 21 days posttreatment ($p < 0.01$ and $p < 0.0001$) compared to saline in SAPAP3 KO mice. Furthermore, in mice who received psilocybin or PME and whose grooming behavior decreased by 10% or more from baseline, were followed up without further treatment at days 28 and 42. PME had a more pronounced effect than psilocybin at 12, 28, and 42 days post-treatment. SAPAP3 KO mice who initially received saline, but did not show an improvement of 10% or more in total grooming scores from baseline received an injection of either psilocybin or PME. Compared to baseline, psilocybin and PME significantly reduced grooming and head/body twitch behavior at 7- and 21 days post-administration ($p < 0.001$). There was no saline control group. PME significantly increased time spent in the center of the open-field test compared to saline ($p < 0.001$) and psilocybin ($p = 0.002$). There was no significant effect on time spent in the periphery. PME significantly increased time spent in the open arm of the elevated plus maze ($p = 0.040$) compared to saline. There was no significant effect of psilocybin. On the marble-burying test both psilocybin and PME increased the number of marbles buried ($p < 0.0001$) compared to saline.

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therefore may have been an unsatisfactory placebo. Moreover, the absence of a significant dose × time interaction on Y-BOCS scores indicates that the observed 1-week dose effect should be interpreted cautiously. An additional limitation was the moderate treatment dose, which was not compared to a higher therapeutic dose (20–30 mg) routinely used in clinical trials for depression (3).

Psilocybin administration in preclinical studies Well-designed preclinical psychedelic studies are advantageous as they are completely devoid of expectancy and placebo effects (22). This is crucial, as even well-designed clinical psychedelic trials that contain a double-blinded placebo control group can be confounded by placebo, as individuals and researchers often know if they received the placebo or the active drug treatment due to the strong perceptual alteration that occur after ingestion of the psychedelic (43). Additionally, in clinical trials such as Schneier *et al*. (2024) (32) and Pellegrini *et al*. (2025) (37), there was substantial psychological support that accompanied psilocybin administration which may have had additional and unique psychological effects (44). Thus, preclinical literature assessing psilocybin administration on obsessive and compulsive-like behaviors may reveal the "true" biological effects of psilocybin devoid of expectancy and placebo effects. Furthermore, recent reviews, highlight

Table 1—*Continued*

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Gattuso *et al*. (2024) (24) **Preclinical genetic knockout mouse model**	Mice were administered with a single dose of psilocybin 1 mg/kg (i.p.) or a saline control.	5 to 7 month old male and female wild-type and SAPAP3 KO mice on a C57BL/6J background. Males: $n = 12$–15 mice per group Females: $n = 6$–12 mice per group	**Locomotor behavior** (conducted for 60 min immediately following injections). **Head-twitch behavior** (conducted for 15 min immediately following drug administration). **Light-dark box** (conducted 1, 3, and 8 days after administration) **Grooming behavior** (conducted 1, 3, and 8 days after administration).	Psilocybin significantly increased the number of head twitches in both WT and SAPAP3 KO mice ($p < 0.0001$). Psilocybin increased locomotion in WT ($p = 0.0001$) but not SAPAP3 KO mice ($p = 0.772$). Psilocybin significantly reduced compulsive grooming behaviour in male KO mice at 3 ($p = 0.010$) and 8 days ($p = 0.016$) after injection. Psilocybin decreased grooming behaviour in both WT and KO female mice ($p = 0.033$) across time points (1, 3, and 8 days after administration).
Lazar *et al*. (2025) (25) **Preclinical genetic knockout mouse model**	**Drug:** Psilocybin dissolved in 0.9% saline; volume 10 μL/g administered intraperitoneally 48 h before testing. **Dose:** 4.4 mg/kg (single injection).	**Baseline phenotyping (Study 1, no drug):** 141 drug-naive juveniles, 11 weeks old at first test. • SAPAP3 KO = 44 (20 males, 20 females). • HET = 42 (21 males and 21 females). • WT = 55 (26 males and 29 females). **Drug experiment (Study 2):** 64 juveniles, 12 weeks at dosing. • SAPAP3 KO = 32 (16 males and 16 females). • WT = 32 (16 males and 16 females).	**Testing schedule:** starting 48 h post-injection, mice were run over consecutive days in this order: • Open–field test (activity and center time). • Elevated plus maze (open–arm time and entries). • Marble–burying test (30 min). • Tube–dominance test (win proportion). • Buried Oreo test (success rate). Only these tasks were repeated because they showed clear genotype effects in Study 1. **Downstream molecular work** – on day 13 after dosing, brains from a VEH subset (11 KO, 13 WT mice) were harvested for synaptic–protein Western blots; psilocybin–treated brains were not analyzed.	**Results from Study 2** **Psilocybin effect:** 4.4 mg kg i.p. produced no main or interaction effect on any behavioral endpoint (three-way ANOVA, all $p > 0.05$). **Hypoactivity persists:** SAPAP3-KO mice traveled far less than WT in the open field ($F = 156.0$, $p < 0.0001$). **Anxiety-like profile:** KO mice spent less time/entries on open arms of the elevated plus maze (*time* $F = 50.97$, $p < 0.0001$; *entries* $F = 24.4$, $p < 0.0001$) and showed reduced center exploration ($F = 11.37$, $p = 0.0013$). **Molecular findings (adult cohort):** male KO mice showed higher GAP43 ($p = 0.001$), synaptophysin ($p = 0.003$) and SV2A ($p < 0.0001$) across brain regions; females showed only SV2A elevation in the frontal cortex ($p = 0.01$). **Reduced burrowing/compulsion**: KO mice buried fewer marbles than WT ($F = 116.2$, $p < 0.0001$). **Enhanced social dominance:** KO mice won more tube-test contests ($F = 18.70$, $p < 0.0001$). **Blunted food-seeking:** KO mice located the buried Oreo in only 25–50% of cases, whereas WT mice succeeded in 87.5%–100% of cases; all genotype differences were statistically significant ($\chi^2 = 5.33$–8.73, $p < 0.05$–0.01). **Sex factor:** no main or interaction effects of sex on any measure (all $p > 0.05$).

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the translatability of mouse models relevant to obsessive and compulsive disorder (specifically the SAPAP3 KO mouse model), where molecular and circuit level mechanisms can be investigated (14, 22).

The marble-burying test (MBT) is a test that exploits rodents spontaneous digging behavior, where a greater number of marbles buried, reflects meaningless repetitive behavior that is characteristic of OCD. Furthermore, frontline pharmacological treatments for OCD such as SSRIs, often decrease marble-burying behavior (45). Using the MBT as a measure of compulsive-like behavior, Matsushima *et al*. (2009) (39) found that psilocybin containing mushrooms (*Phlebotomus argentipes*) at a dose of 0.1–1 g/kg acutely reduced the number of marbles buried in the MBT in 5-week-old male ICR mice. Similarly, psilocybin (1.5 mg/kg, oral) significantly reduced marble burying behavior but to a lesser degree then *P.* argentipes, especially at lower doses. Odland *et al*. (2021) (40) found that psilocybin (1 and 2 mg/kg, i.p.) significantly reduced marble-burying behavior (MBT was conducted 15 min after injection) in female NMRI mice, which was not mediated by activation of the 5-HT_{2A} and 5-HT_{2C} receptors. This effect was aligned with findings in a different mouse strain, sex and dose, where Singh *et al*. (2023) (41) administered a single dose of psilocybin (4.4 mg/kg, i.p.) 30 min before the MBT in male wild-type (WT) ICR mice and found that psilocybin acutely decreased marble burying compared to vehicle; however, this effect did not persist until day 7. This acute reduction in marble-burying behavior was independent of the 5-HT_{2A} and 5-HT_{1A} receptor.

However, it is important to note that the MBT has been critiqued as a model of compulsive-like behavior with concerns around its predictive

Table 1—*Continued*

Study	Treatment	Sample Characteristics	Relevant Outcome Measures	Outcome Measures (Results)
Gattuso *et al.* (2025) (26) **Preclinical genetic knockout mouse model**	Mice received psilocybin dissolved in water via oral gavage (10 mL/kg, pH ~7), with vehicle-treated controls receiving water alone. Two doses were tested (0.1 mg/kg and 1 mg/kg), administered 5 days per week for 5 weeks. A final dose was delivered 24 h prior to culling. Note: The first oral gavage was conducted on day 0.	4 to 7 months old male and female WT and SAPAP3 KO mice on a C57BL/6J background. Males: $n = 6–8$ mice per group. Females: $n = 7–11$ mice per group.	**Locomotor behavior** (day 0 and day 10) **Head-twitch response** (day 0 and day 10) **Social interaction test** (days 21 – 25) **Light-dark box** (day 28) **Pre-pulse Inhibition** (day 29) **Gut transit time** (day 30) **Porsolt swim test** (day 32) **Gut microbiome 16sRNA sequencing** (day 28). Locomotor behavior and head-twitch response was conducted for 15 and 30 min respectively, 30 min after oral gavage. All other behaviors were conducted approximately 24 h after the last dose.	**Locomotor activity:** Psilocybin (1 mg/kg) increased locomotion acutely in WT mice ($p < 0.001$) and across all groups after repeated dosing ($p = 0.002$). **Head-twitch response** Both 0.1 and 1 mg/kg psilocybin increased head-twitches in males and females ($p < 0.0001$) in a dose-dependent manner. There was no time x treatment effects ($p = 0.311$). **Three-chamber test:** SAPAP3 KO mice displayed reduced sociability/social novelty ($p < 0.0001$ and $p = 0.015$); psilocybin (1 mg/kg) increased sociability in male WT mice ($p = 0.009$). **Light-dark box:** SAPAP3 KO mice showed anxiety-like behavior (reduced light duration) ($p < 0.0001$) unaffected by psilocybin 0.1 or 1 mg/kg ($p = 0.872$ and $p > 0.999$). **Grooming behavior:** SAPAP3 KO mice exhibited compulsive-like grooming ($p < 0.0001$), with no significant effect of psilocybin 0.1 or 1 mg/kg ($p = 0.978$ and $p = 0.803$). **Pre-pulse inhibition:** Psilocybin 0.1 and 1 mg/kg did not alter pre-pulse inhibition ($p = 0.622$, $p = 0.895$); however, 1 mg/kg reduced acoustic startle response in male mice ($p = 0.017$). There was no genotype effect ($p = 0.680$). **Gut-transit time:** Psilocybin dose-dependently increased gut transit time ($p = 0.034$ and $p = 0.003$). No genotype differences ($p = 0.382$). **Porsolt Swim Test (PST):** No genotype differences in immobility ($p = 0.116$); psilocybin had no effect ($p = 0.726$). **Gut microbiome:** There was no genotype or treatment effect on alpha or beta diversity. However, at the species level, psilocybin decreased the abundance of several *Lactobacillus* and *Alistipes species* only in male wild-type mice.

and construct validity (45). Additionally, all of these studies utilized WT mice only (rather than a mouse model of OCD such as SAPAP3 KO mice) which complicates interpretation as psilocybin's effect may not be anti-compulsive but could be a more generalized effect. For instance, in WT mice, marble burying is also related to exploratory behavior, thus, a psilocybin effect in WT mice may not be purely anti-compulsive but may indicate, anxiolysis or reduced motivation. However, overcoming these limitations, Brownstien *et al*. (2024) (23) and Gattuso *et al*. (2024) (24) investigated how acute psilocybin administration alters compulsive grooming behavior in the SAPAP3 KO mouse model. The SAPAP3 KO mouse model is arguably the most well-validated animal model of OCD (46). SAPAP3 KO mice lack the SAPAP3 protein, a postsynaptic protein, involved in the regulating and trafficking of excitatory neurotransmitter receptors and highly expressed in the striatum. The human ortholog of SAPAP3 (DLGAP3) has been implicated in patients with OCD (47) and pathological grooming (48) and mice display cortico-striatal dysfunction that recapitulates the circuit-level abnormalities observed in humans (49, 50). Furthermore, these mice display a repetitive and harmful excessive grooming phenotype which if left untreated will cause skin lesions (51). Thus, the excessive grooming is compulsive because, despite the behavior causing self-harm, the mice cannot stop. Additionally, these mice also display excessive anxiety-like behavior and tic-like behavior which respond to front-line pharmacological treatments relevant to OCD and OCRD (51, 52).

Both Brownstien *et al*. (2024) (23) and Gattuso *et al*. (2024) (24) found that psilocybin (4.4 and 1 mg/kg, i.p., respectively) led to enduring reductions (between 1 and 7 weeks postinjection) in excessive grooming behavior in SAPAP3 KO mice. These data suggest that psilocybin has anti-compulsive effects that are independent of placebo. Furthermore, the reliability of the findings that psilocybin can lead to enduring reductions in compulsive-like behavior is strengthened by independent labs using different doses and time points (53). Whereas Brownstien *et al*. (2024) (23) and Gattuso *et al*. (2024) (24) did not assess the immediate effects of psilocybin on excessive grooming behavior, Sard *et al*. (2005) (38) demonstrated that psilocybin (0.5 mg/kg, i.p.) rapidly reduced 5-HT–induced

scratching behavior in Swiss-Webster mice and, importantly, provided novel structure–activity relationship insights into the anti-compulsive potential of psilocybin analogues. The study identified 1-methylpsilocin as a selective 5-HT_{2C} agonist with minimal 5-HT_{2A} activity and an inverse agonist profile at 5-HT_{2B}, suggesting both therapeutic relevance and an improved safety profile. Its phosphate prodrug, 1-methylpsilocybin, showed strong in vivo efficacy in the scratching model, comparable to psilocybin itself, indicating the translational value of prodrug approaches. Similarly, 4-fluoro-N,N-dimethyltryptamine produced robust antiscratching effects, possibly due to enhanced blood–brain barrier penetration despite only modest in vitro 5-HT_{2C} activity. By contrast, compounds with bulkier substitutions (e.g., N-butylpsilocin) were largely inactive, underscoring the importance of structural constraints at the 1-position for 5-HT_{2C} selectivity. Collectively, these findings highlight that psilocybin's anticompulsive effects may be mediated via 5-HT_{2C} receptor activity and that rational modification of its structure could yield compounds with greater selectivity and potentially superior therapeutic profiles for OCD and related disorders.

Interestingly, Brownstien *et al*. (2024) (23) found that psilocybin and psychedelic mushroom extract (PME) increased marble-burying behavior in SAPAP3 KO mice and KO mice had reduced marble burying compared to WT mice at baseline, supporting concerns surrounding the validity of this behavioral test for compulsive-like behavior (45). The authors contend that psilocybin and PME increased marble burying in SAPAP3 KO mice because these animals display abnormally low baseline marble burying due to heightened anxiety. They argue that by reducing anxiety, the treatments restored normal exploratory and digging behaviors, making the increase in marble burying a reflection of behavioral normalization rather than enhanced compulsivity. However, in Brownstein *et al*. (2024) (23), only PME (and not psilocybin) significantly altered anxiety-related measures, whereas both compounds significantly increased marble burying. Thus, we contend that excessive grooming in SAPAP3 KO mice may monopolize the behavioral repertoire and suppress other behaviors, including digging. By reducing pathological grooming, psilocybin and PME may have reallocated behavioral capacity, thereby enabling mice to engage in more typical exploratory and digging activity.

Interestingly, psilocybin did not alter marble-burying behavior in younger SAPAP3 KO mice which have less severe compulsive grooming behavior (25). Notably, Brownstien *et al*. (2024) (23) reported that psilocybin and PME produced long-term reductions in head and body twitches, behaviors proposed to model tic-like activity in SAPAP3 KO mice (52). These findings suggest that psilocybin could hold therapeutic potential for Tourette syndrome, a disorder also marked by compulsive features, thereby supporting its broader applicability across the OCRD spectrum. Interestingly, psilocybin did not attenuate the excessive anxiety-like phenotype in SAPAP3 KO mice (23, 24), but PME did (23), possibly due to entourage effects.

The majority of preclinical studies reviewed here used only one dose of psilocybin administration; however, both Kiilerich *et al*. (2023) (42) and Gattuso *et al*. (2025) (26) assessed the effects of chronic psilocybin administration on compulsive-like behavior. Kiilerich *et al*. (2023) found that male Long-Evans rats that received psilocybin (0.05 mg/kg, s.c.) every second day for 3 weeks had significantly reduced self-grooming behavior the second day after the last psilocybin dose. Importantly, this dose of psilocybin (0.05 mg/kg, s.c.) did not induce any hallucinogenic-like behavior. Interestingly, the researchers also found that chronic low-dose psilocybin increased the expression of the 5-HT_7 receptor and the synaptic vesicle protein 2A (SV2A: a proposed marker for synaptic density) in the paraventricular thalamus. As 5-HT_7 receptors and SV2A are located presynaptically, this suggests that chronic low-dose psilocybin is increasing synaptic input into the paraventricular thalamus compared to control. Due to the reasons mentioned above (i.e., less parsimonious findings when using WT rodents), Gattuso *et al*. (2025) (26) decided to investigate the effects of chronic administration of psilocybin 0.1 mg/kg and 1 mg/kg in SAPAP3 KO mice. They found that 20 doses of psilocybin 0.1 mg/kg and 1 mg/kg (oral) did not ameliorate the excessive anxiety or grooming phenotype in SAPAP3 KO mice. The absence of an effect was unlikely due to tolerance as the head twitch response did not diminish after chronic compared to acute administration. Additionally, 20 doses of psilocybin 1 mg/kg did not significantly alter the gut microbiome of SAPAP3 KO animals.

Methodological limitations of included preclinical studies One key caveat in modelling OCD and OCRD preclinically, is the inability to assess effects on obsessional behaviors in rodents because obsessions are defined as intrusive, unwanted, and repetitive thoughts or urges, which inherently require subjective reporting and internal experience. Animals cannot communicate internal thought processes or mental experiences, so obsessions cannot be directly measured or reliably inferred in rodents.

In contrast, compulsions are overt, observable, repetitive behaviors intended to alleviate distress or anxiety associated with obsessions. Such behaviors (e.g., excessive grooming, repetitive checking, or stereotyped patterns) can be objectively quantified and analyzed in rodents.

Therefore, preclinical mouse models focus primarily on compulsive-like behaviors, as these behaviors provide a measurable and operationally defined endpoint that can be consistently observed, quantified, and experimentally manipulated. However, according to current diagnostic criteria (although rare), it is possible for individuals to be diagnosed with having only obsessional or compulsive behavior (rather than both) (11) and so clinical studies are needed to assess psilocybin's effect on obsessions.

Synthesizing clinical and preclinical findings Overall, the evidence suggests that psilocybin administration has the potential for reducing obsessive symptoms and compulsive behaviors and is relevant to a variety of neuropsychiatric disorders across the OCRD spectrum. Of the disorders across the OCRD spectrum, psilocybin has been most thoroughly investigated for OCD. Preclinical evidence suggests that psilocybin exhibits anticompulsive effects that are independent of placebo and expectancy effects. These effects can be both rapid (38, 40, 41) and enduring (23, 24). However, the exact mechanisms by which psilocybin reduced compulsive behavior have been underexplored. For instance, both Brownstien *et al*. (2024) (23) and Gattuso *et al*. (2024) (24) did not assess which receptors could be mediating the reduction in compulsive-like behavior in SAPAP3 KO mice. Such findings could provide critical evidence to support or refute the hypothesis that these serotonergic receptors are directly involved in the anti-compulsive-like effects of psilocybin especially as studies have found that psilocybin can reduce rodent marble-burying independently of 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptor activation (40, 41). Figure 3 indicates that psilocybin's therapeutic effects in animal models relevant to OCRD has consistently been shown to be independent of the 5-HT_{2A} receptor; however, future well-designed experiments are needed.

As hallucinogenic-like behavior in rodents and psychedelic experiences in humans is mediated by the 5-HT_{2A} receptor (54, 55) follow-up receptor antagonism studies could elucidate if the hallucinogenic experience is necessary for the anti-compulsive effects of psilocybin. Additionally, preclinical evidence from Kiilerich *et al*. (2023) (42) suggests that repeated subhallucinogenic dosing may have beneficial effects on compulsive-like behavior. Thus, future studies should continue to investigate whether pretreatment with a highly selective 5-HT_{2A} antagonist such as MDL-100,907 (Volinanserin) abolishes the anti-compulsive effect of a single hallucinogenic dose of psilocybin in a mouse model of OCD and whether nonhallucinogenic psychedelic analogs can reduce compulsive-like behavior. If further preclinical evidence suggests that psilocybin can retain its anticompulsive effects at the preclinical level independent of 5-HT_{2A} receptor activation, then it would be logical to conduct similar studies in clinical populations. If a reduction in obsessive and compulsive symptoms is independent of the psychedelic experience, this treatment would be more scalable as there would be a reduced need for clinical supervisions and, therefore, less financial barriers, improved safety and tolerability, and better patient acceptance and adherence as some individuals may prefer treatments without an intense psychedelic experience due to personal, cultural, or psychological reservation.

Although further research is needed to explore different chronic dosing paradigms, the findings of Gattuso *et al*. (2025) (26) suggest that acute psilocybin administration may have greater therapeutic efficacy for compulsive-like behavior. Moreover, since psilocybin did not alter the gut

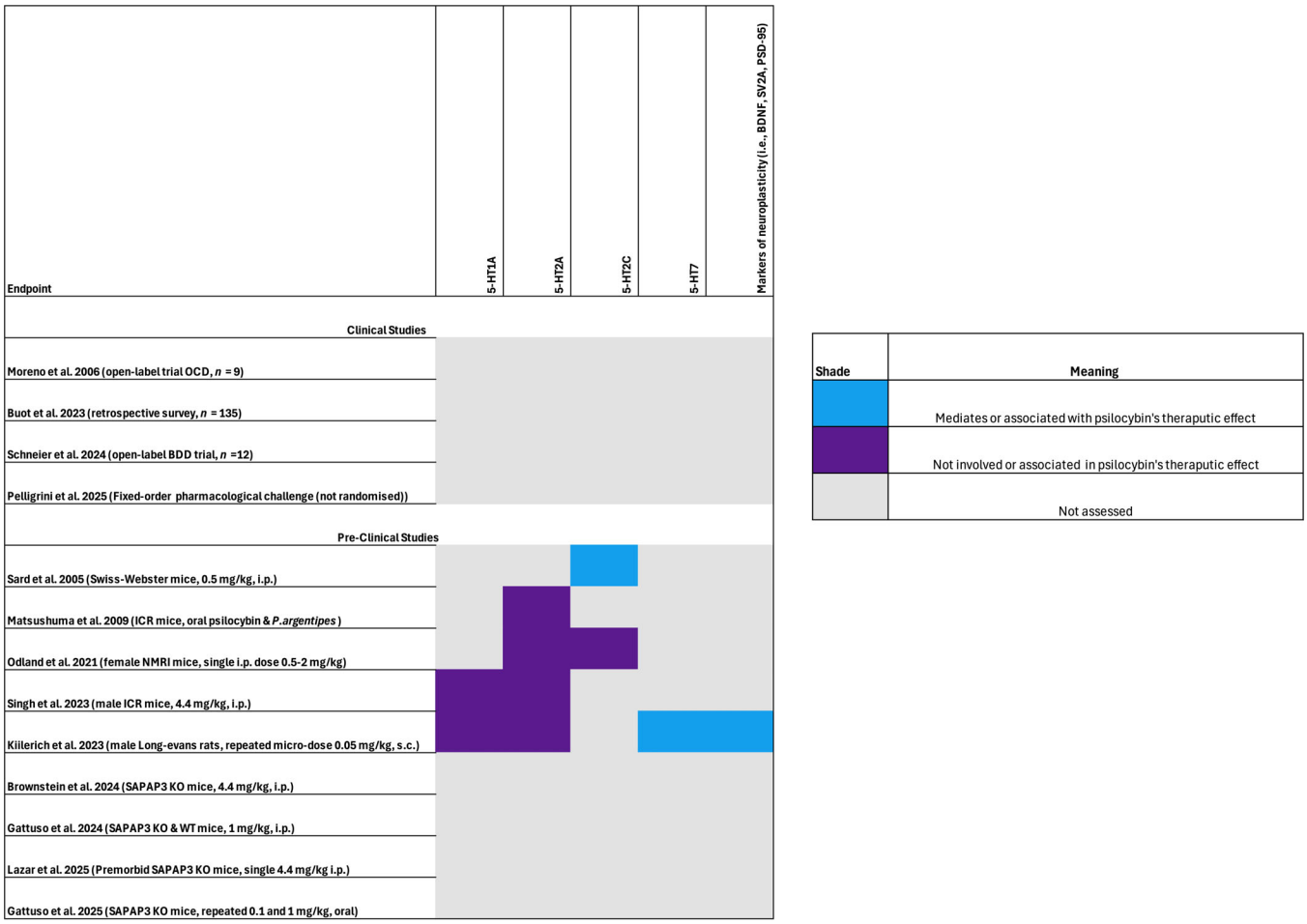

Figure 3. Cross-study heat map of mechanistic endpoints assessed following psilocybin administration. Rows list the 13 primary studies reviewed (4 clinical at top, 9 preclinical beneath, ordered chronologically. Blue shading indicates that the receptor or mechanism was implicated in mediating or being associated with psilocybin's effects, purple shading indicates that it was not involved or associated, and gray shading indicates that the endpoint was not assessed.

microbiome in the SAPAP3 KO mouse model, future studies could investigate the use of probiotics as an adjunctive treatment to enhance psilocybin's anti-compulsive effects, particularly given evidence that probiotics can reduce obsessive-compulsive–like behaviors (56).

Psilocybin's effect on neuroplasticity relevant to OCRD There is a relative paucity of studies directly investigating the cellular mechanisms by which psilocybin exerts therapeutic effects in animal models of OCRDs (Figure 3; Table 1). Addressing this gap is critical for developing targeted therapeutics. We hypothesize that psilocybin's long-term benefits in reducing compulsive-like behavior are mediated through its ability to induce rapid and sustained alterations in neuronal morphology and synaptic signaling. Below, we outline evidence for psilocybin-induced neuroplasticity across molecular, cellular, synaptic, and behavioral levels**,** highlighting their potential translational relevance for OCD.

Molecular level Moliner *et al*. (2023) reported that psilocybin's neuroplastic effects may involve positive allosteric modulation of TrkB signalling, independent of 5-HT_{2A} receptor activation, suggesting an alternative mechanism through which psychedelics might enhance cortical plasticity. However, these findings have not yet been independently replicated, and subsequent evidence has called this mechanism into question. Jain et al. (2025) (57) directly tested whether classical psychedelics, including psilocin and LSD, interact with TrkB using a live-cell reporter assay and found no evidence of agonist or allosteric modulation of TrkB. Taken together, while TrkB involvement remains an intriguing possibility, the precise nature of psilocin's interaction with TrkB remains unclear, and further research is needed to determine whether psychedelic-induced plasticity occurs through direct modulation of TrkB signaling or via distinct molecular pathways.

In the mouse cortex, psilocybin-evoked c-Fos expression was strongly correlated with endogenous *Grin2a* and *Grin2b* (58). As SAPAP3 KO mice exhibit altered NMDA receptor subunit expression and function in the striatum compared to WT mice (51), it is possible that psilocybin's downstream interactions with glutamatergic signaling could normalize NMDA receptor function. Testing this empirically and determining whether such normalization translates into reduced compulsive behaviors, represents an exciting future direction.

Preclinical studies demonstrate that psilocybin induces rapid, region-specific transcriptional changes consistent with enhanced neuroplasticity. Jefsen *et al*. (2021) (59) showed that acute psilocybin robustly upregulated immediate early genes (e.g., *c-Fos, Junb*, and *Nr4a1*) and plasticity-related transcripts (e.g., *Sgk1 and Psd-95*) in the prefrontal cortex, with more modest effects in the hippocampus. Similarly, Fadhunsi *et al*. (60) found widespread acute transcriptional alterations in the prefrontal cortex, including regulation of *BDNF, Negr1*, and *neuroplastin*, but no persistent changes at 4 weeks. Together, these findings highlight psilocybin's capacity to rapidly engage molecular programs of plasticity, particularly in the prefrontal cortex—a key node in the corticostriatal circuits implicated in OCRDs. By transiently reshaping these molecular pathways, psilocybin may facilitate long-term normalization

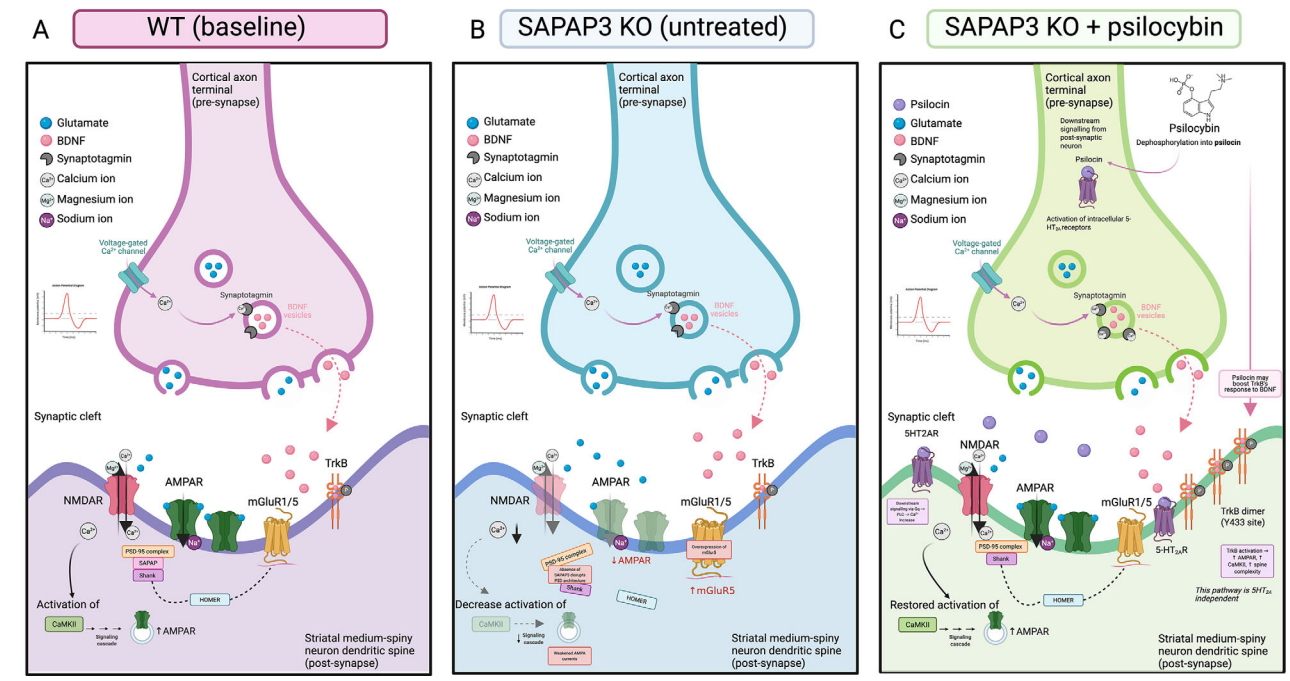

Figure 4. Synaptic structure and function in WT, SAPAP3 KO, and psilocybin-treated SAPAP3 KO mice. (A) Wild-type (WT) mice: At the presynaptic terminal, action potentials open voltage gated calcium channels (VGCCs), allowing Ca^{2+} influx. Calcium binds to synaptotagmin, triggering vesicle fusion and the release of brain-derived neurotrophic factor (BDNF) and glutamate into the synaptic cleft. Glutamate activates postsynaptic AMPA and NMDA receptors (AMPAR and NMDAR). AMPAR-mediated Na^{+} influx depolarizes the dendritic spine, relieving the Mg^{2+} block on NMDAR's and allowing Ca^{2+} entry. These receptors are anchored by the postsynaptic scaffold composed of PSD-95, SAPAP3, Shank, and Homer proteins which play a crucial role in synaptic plasticity (61, 62). BDNF bind to TrkB receptors, activating CaMKII and supporting synaptic plasticity (63, 64). mGluR5 modulates additional metabotropic signaling (65). (B) SAPAP3 knockout (KO) mice (untreated): There is no direct evidence that BDNF release is reduced in SAPAP3 KO mice, but changes to the postsynaptic structure may affect how BDNF signals through its receptor, TrkB. Without SAPAP3, the scaffold that holds key receptors like AMPARs and NMDARs together becomes unstable due to the poor receptor anchoring (51, 66). This increases mGluR5 activity and weakens AMPAR signaling (66, 67). As a result, this could lead to impaired synaptic plasticity and behavior (66–69). (C) Psilocybin treated SAPAP3 KO mice: Psilocybin normalizes presynaptic Ca^{2+} influx and restores glutamate release via synaptotagmin-dependent exocytosis (70). In the synaptic cleft, psilocin may bind directly to TrkB dimers, stabilizing them in a conformation that enhances responsiveness to endogenous BDNF, however, evidence is mixed (Jain *et al.* (2025) (57). Psilocin also accesses both surface and intracellular 5-HT_{2A} receptor pools. 5-HT_{2A} receptors mediate hallucinogenic responses (70) and contribute to structural plasticity (6). Despite this, psilocybin-induced plasticity may occurs independently of the 5-HT_{2A} receptor via direct TrkB activation (7). Postsynaptically, TrkB signaling re-engages CaMKII and promotes AMPAR trafficking, potentially rescuing aspects of the disrupted postsynaptic scaffold and potentially mediating long-term therapeutic behavioral outcomes (7, 23, 24, 71). Created in https://BioRender.com

of dysregulated frontostriatal connectivity that underlies compulsive symptomatology.

Cellular level At the cellular level, psilocybin promotes neuronal proliferation, differentiation, and maturation (72, 73). These processes support long-term circuit remodeling, potentially reversing cellular plasticity deficits observed in OCD models. For example, SAPAP3 KO mice, which display striatal plasticity impairments (45–47), may be particularly responsive to psilocybin's neuroplastic effects.

Synaptic level Psilocybin induces dendritic plasticity, including increased spine density in the medial prefrontal cortex (73, 74). Jefsen *et al.* (2021) (59) found that psilocybin increased the expression of PSD-95 in the rat prefrontal cortex which is a postsynaptic scaffolding protein which is crucial for synaptic plasticity and excitatory neurotransmission (75).

Shao *et al.* 2021 (74) demonstrated that psilocybin not only increases dendritic spine density but also enhances excitatory neurotransmission in layer 5 pyramidal neurons of the medial frontal cortex, as reflected by elevated miniature excitatory postsynaptic current frequency and a trend toward increased amplitude. These electrophysiological findings provide functional evidence of psilocybin-induced synaptic plasticity, complementing structural spine remodeling.

Together, these synaptic modifications may underpin lasting improvements in compulsive behavior. Experimentally, this could be probed by measuring prefrontal and striatal expression of PSD-95, synaptophysin, and BDNF following psilocybin treatment in SAPAP3 KO mice, linking synaptic changes to behavioral outcomes. To determine whether psilocybin's effects on dendritic spine growth causally mediate reductions in compulsive-like behavior, future studies could employ spine-specific photoablation approaches (e.g., (76)), enabling selective elimination of newly formed spines while assessing behavioral outcomes.

Behavioral level At the behavioral level, the observation that psilocybin produces enduring reductions in compulsive-like behavior for up to 1–7 weeks after a single dose (23, 24) suggests that it may induce long-lasting structural changes in the brain. However, this possibility requires empirical verification using a well-validated mouse model of compulsive-like behavior. Based on the findings of this systematic review, we hypothesize that psilocybin normalizes aberrant striatal plasticity through coordinated molecular, cellular, and synaptic mechanisms, thereby restoring balanced corticostriatal circuit function and promoting sustained therapeutic effects (Figure 4).

Future clinical directions

Future clinical research should prioritize randomized, placebo-controlled trials with sufficient sample sizes to determine psilocybin's true efficacy in OCD and related disorders. Furthermore, we encourage the use of psychedelic-naïve participants and an active placebo control, such as niacin or methylphenidate, which can produce somatic symptoms such as tingling and euphoria, respectively, which could be confused with the somatic symptoms of psychedelics (particularly in psychedelic-naïve participants). Additionally, the studies should compare different dosing strategies—single high doses versus repeated low doses—and examine psilocybin's neural effects in patients with OCD using functional neuroimaging. Neuroimaging studies in healthy participants have demonstrated that psilocybin acutely influences brain regions implicated in OCD pathophysiology. For example, functional magnetic resonance imaging (fMRI) revealed that healthy controls administered psilocybin exhibited acute reductions in blood oxygen level-dependent signal and cerebral blood flow within fronto-temporo-parietal areas and key connectivity hubs, including the thalamus, putamen (striatum), and midline cortex (anterior and posterior cingulate cortices) (77). Notably, these regions show hyperactivity in patients with OCD (78).

Furthermore, future studies could systematically investigate the synergistic effects of combining psilocybin treatment with structured psychotherapy, particularly exposure and response prevention (ERP), for patients with OCD. Although current clinical trials already incorporate psychotherapeutic support, controlled comparisons could clarify how psilocybin may enhance cognitive flexibility and engagement with therapeutic tasks, potentially accelerating treatment gains (32, 79). Structured integration of psilocybin with ERP in clinical protocols could harness both biological and psychological mechanisms.

Addressing some of these future directions, Ching *et al*. (2023) (80) have published a study protocol assessing the clinical and neural effects of a single dose of psilocybin in patients with OCD in a randomized, double-blind placebo-controlled trial (using the active control – niacin). The researchers are using fMRI to assess how psilocybin alters fronto-striatal circuitry in patients with OCD and if normalization of this circuitry is associated with reductions in OCD symptomatology. The study is more well powered than Pellegrini *et al*. (2025) (37) with a plan to enroll 36 participants. The studies end point will be assessing symptoms and neural changes 48 h after the last dose. This study is an exciting future direction that will further elucidate the potential role of psilocybin treatment for patients with OCD. We encourage additional studies to assess the enduring effects of psilocybin on OCD symptomatology and neural changes from 1 to 12 months based on the sustained therapeutic effects of psilocybin in preclinical animal models of OCD and psilocybin's long-lasting effect in other patient populations (81–83).

It is important to note out of the 9 preclinical studies, only 2 studies (24, 26) comprehensively analyzed sex as an important biological variable. Out of the 3 clinical studies, merely one study (36) was powered enough to investigate sex differences, which found minimal sex differences.

In alignment with Shadani *et al*. (2024) (84) we strongly encourage future researchers to consider sex as an important biological variable in psilocybin research, to develop more targeted interventions, especially since Gattuso *et al*. (2024, 2025) (24, 26, 85) has found sex-specific responses to psilocybin.

The findings that psilocybin had therapeutic effects in SAPAP3 KO mice (23, 24), a mouse model relevant not just to OCD but across the OCRD spectrum (52), coupled with the promising improvement in BDD symptoms following psilocybin (32), suggests that future research should also expand to include disorders with overlapping neurobiological features, such as trichotillomania, dermatilomania, and hoarding disorder, where compulsivity is a core element (11).

Finally, preclinical evidence suggests that mushroom extract containing psilocybin may yield superior efficacy when compared to isolated psilocybin (23, 39) for behaviors relevant to OCD, most likely due to entourage effects through additional biologically active compounds such as baeocystin and norbaeocystin. Administering psilocybin-containing mushrooms to patients with OCD and related disorders and comparing effects to isolated psilocybin would be an exciting and worthwhile avenue of investigation.

Conclusions

This comprehensive review highlights psilocybin as a promising therapeutic candidate for OCD and related disorders. Across clinical and preclinical studies, psilocybin has demonstrated the capacity to reduce obsessive symptoms and compulsive behaviors, with both rapid (clinical) and enduring (preclinical) effects. While early clinical trials are constrained by small sample sizes and methodological limitations, converging evidence from animal models—particularly those employing the SAPAP3 KO mice—indicates robust anti-compulsive effects that are independent of placebo or expectancy influences.

Mechanistically, emerging data suggest that psilocybin may exert its long-term therapeutic effects (in other disorders, but also presumably OCD) through the induction of neuroplasticity. Notably, some neuroplastic effects appear to be independent of hallucinogenic-like behavior, raising the possibility that non-hallucinogenic psychedelic analogs or subperceptual dosing regimens may retain therapeutic efficacy while enhancing scalability and patient acceptability.

Future research should focus on well-powered, placebo-controlled clinical trials, detailed mechanistic studies in validated animal models, and investigations into the role of sex, symptom dimensions, and dosing paradigms. Given the consistency of findings across models and the transdiagnostic relevance of compulsivity, psilocybin-based interventions may offer a novel and scalable approach for treating OCRDs. For instance, Gattuso *et al*. (2024) (24) found that administration of psilocybin 1 mg/kg reduced compulsive grooming, with effects persisting for up to 8 days in male KO mice but proving more transient in female KO mice which aligns with clinical data from Pellegrini *et al*. (2025) (37). Pellegrini *et al*. (2025) (37) reported that a single 10 mg dose of psilocy—binapproximately comparable to the dose used in our study—led to a significant reduction in OCD symptomatology, primarily driven by compulsions, with effects most sustained in males at four weeks. This cross-species convergence adds further credence for the use of screening potential novel therapeutics for compulsive behavior using the SAPAP3 KO mouse model.

This review has systematically synthesized the existing scientific literature, critically identified current limitations and gaps, and provided informed guidance for future research directions—thereby advancing the development of effective and scalable therapeutic interventions for individuals suffering from OCD and related disorders.

Methods

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (21) for transparent and comprehensive reporting and was in alignment with previously published systematic reviews (22, 86). J.J.G. conducted an electronic search on the PubMed database on March 21, 2025 using the following search string: (psilocybin OR psilocin OR "magic mushrooms" OR psychedelic OR psychedelics) AND ("obsessive compulsive disorder" OR OCD OR compulsive OR compulsion OR compulsions OR obsessive OR obsession OR obsessions OR "obsessive-compulsive" OR compulsive-like). A second search was conducted on September 17, 2025, during the peer-review process.

Articles were excluded by J.J.G. or B.B., if they were not an original article (i.e., reviews, book chapters, editorials, study protocol, and conference abstracts), were not in English, did not administer psilocybin, psilocin or psilocybin containing mushrooms, were not peer reviewed (i.e., preprints) or did not assess obsessive and/or compulsive behavior. The primary variables extracted where the main outcomes measures related to behavioral testing (and molecular and neural mechanisms where appropriate) (Table 1). Furthermore, descriptive statistics such as sample size, age, sex and dose were included where possible.

Author contributions

J.J.G. conducted the systematic review and wrote the manuscript and generated Figures 1 and 3. B.B. helped with the systematic search, Table 1 and generated Figures 2 and 4. C.W. helped with writing on the manuscript. K.H. helped with Table 1. T.R. and A.J.H. helped with supervision, manuscript revision and funding.

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Author disclosures

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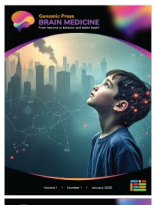

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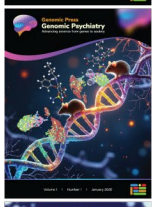

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