Animal models in psychedelic research – Tripping over translation

Muad Y. Abd El Hay[1,✉], **Ana Cukić**[1], **Marieke L. Schölvinck**[1,*], **and Martha N. Havenith**[1,*]

[1]Ernst Strüngmann Institute (ESI) gGmbH of the Max Planck Society, Deutschordenstr. 46, 60528 Frankfurt a.M., Germany
[*]These authors contributed equally

Psychedelic substances show promise for treating psychiatric disorders including depression, anxiety, and PTSD, yet the neurobiological mechanisms underlying their therapeutic effects remain poorly understood. Preclinical animal research, essential for elucidating circuit-level mechanisms, has yielded inconsistent results. We argue this translational gap stems from systematic disconnects between conditions determining therapeutic outcomes in humans and those employed in animal research. Our analysis of 106 rodent psychedelic studies (2019-2024) combined a systematic audit of experimental conditions with a framework-based evaluation of behavioural assays. First, we assessed adherence to welfare practices paralleling "set and setting" factors critical to human therapy, finding that most studies employ stress-inducing conditions: testing during inactive circadian phases (82%), barren housing (89%), injection-based administration (100%), and forceful handling (77%). Second, we evaluated the capacity of behavioural assays to capture experiential dynamics, revealing that most studies rely on brief, constrained testing with isolated behavioural markers that fail to capture the multidimensional, temporally evolving nature of psychedelic states. Beyond these methodological gaps, we identify a third critical factor largely absent from preclinical research: individual differences and social context. Most animal studies use group-level, cross-sectional designs that cannot characterize heterogeneous treatment responses or social mechanisms implicated in therapeutic change. We propose that improving translation requires a fundamental reorientation: from brief testing of stressed, isolated animals toward longitudinal tracking of individuals in enriched social environments using comprehensive behavioural characterization.

Introduction

Mental disorders such as depression and anxiety impact the lives of an ever growing number of people, often in persistent and debilitating ways. Globally, depression affects a staggering 280 million people (1). Yet despite decades of research and pharmaceutical development, nearly 40 % of all patients with depression fail to respond to available treatments (2). This situation necessitates new treatment approaches to mental disorders that go beyond conventional drug development paradigms.

Among the most promising new alternatives, psychedelic substances have emerged as potential therapeutic tools. Substances like psilocybin, LSD, and MDMA, some of which have been used in traditional practices for centuries, are the subject of 488 clinical trials to date – tendency rising (3). These trials show that psilocybin has therapeutic efficacy comparable to established antidepressants, with a notably favourable side effect profile (4). Importantly, these effects extend even to patients that were deemed 'treatment-resistant' (5), and they apply across a wide range of prominent mental disorders including anxiety, post-traumatic stress disorder (PTSD), and even addiction (6–8) – a broad applicability that is uncommon for classical treatments. Moreover, therapeutic changes are typically achieved in only one or two dosing sessions, yet produce long-lasting improvements (4).

Together, these properties position psychedelic substances as a potential 'therapeutic multitool', addressing a wide variety of mental ailments, often in a one-shot treatment. What processes allow psychedelics to trigger such substantial changes in neuronal processing in such a short time, and across vastly different mental health conditions? At a global level, psychedelic substances have been shown to disrupt ordinary brain organization through widespread desynchronization, decreasing activity in the default mode network while dissolving boundaries between typically segregated brain regions (9–11). But how are such global shifts in neuronal circuit communication produced at the circuit level, and how do they in turn translate to lasting therapeutic changes? To date, these questions remain largely unresolved, and due to their non-invasive nature, human brain recordings lack the necessary spatial or temporal resolution to tackle them directly. As such, we must study the neuronal circuit mechanisms of psychedelics in animal models. Given their potential for detailed circuit-level recordings and controlled behavioural testing, animal models are essential for drawing mechanistic links between acute shifts in neuronal circuitry triggered by psychedelics, and their long-term effects. However, psychedelic research in animal models has so far mainly succeeded in establishing receptor signaling pathways and acute neuroplasticity markers, whereas the factors that determine therapeutic outcomes in humans—including the critical role of context, the predictive significance of acute experiential quality, and the substantial heterogeneity in treatment response—have largely remained unaddressed.

In this analysis of the field, we argue that the successful translation of psychedelic research from animal models to human psychedelic therapy hinges on three factors that are well established in clinical research, but have been largely overlooked in preclinical studies: (1) The importance of set and setting (the psychological mindset and environmental context in which psychedelics are administered), (2) The central role of subjective experiences for acute and long-term effects, and (3) The

significance of inter-individual differences for therapy outcomes. We will examine how current animal models address each of these factors, and propose methodological advances that could improve translation between preclinical findings and clinical outcomes.

Set and Setting

The concept of "set and setting" has been recognized as a critical determinant of subjective experiences and therapeutic outcomes in human psychedelic research. "Set" refers to the individual's mindset, expectations and emotional state, while "setting" refers to the physical and social environment in which the psychedelic experience occurs. A strong therapeutic alliance and a mental state of surrender positively influence therapeutic outcomes by encouraging deeper psychedelic experiences (12–14), while feelings of preoccupation prior to a psychedelic session as well as greater anxiety during the experience predict less favourable clinical outcomes (14, 15). Additionally, self-reports from recreational users show a strong correlation between feelings of safety during the experience and positive long-term effects (16). The importance of context in psychedelic therapy has led to the development of standardized reporting guidelines (17), as well as a set of recommendations to increase the likelihood of favorable outcomes and reduce the chances for adverse effects (18).

Given the importance of environmental, psychological and experiential factors in human psychedelic therapy, we examined whether preclinical studies account for analogous considerations in animal models.

Rodents are the most commonly used animal models in translational research on psychedelics. Initial findings suggest that psychedelic episodes in rodents show context effects and subjective distortions that closely model mechanisms encountered in humans (19–22). This suggests that "set and setting" factors are also crucial in animal models in order to capture therapeutically relevant psychedelic processes. We therefore systematically examined how psychedelic research has implemented key welfare practices by analysing the housing, handling, and experimental conditions in 106 rodent studies published from 2019-2024 (Supplementary Fig. S2).

Circadian alignment. Consistent with research in humans, research in rodents has shown that the circadian phase of testing can substantially influence behavioural outcomes. Locomotor activity is consistently higher during the dark (active) phase, while effects on social behaviour and cognitive performance are more task-dependent (23–25). Rodents are predominantly nocturnal animals, with peak activity occurring during the dark phase of the light/dark cycle. Yet of the 106 psychedelic studies we analysed (Figure 1), only 19 explicitly reported housing rodents under a reversed light/dark cycle to enable active-phase testing, while 82 studies adhered to a standard cycle, and 5 omitting this information. This indicates that the majority of psychedelic experiments in rodents were conducted during their inactive (sleep) phase. This mismatch likely contributes to poor translation of preclinical findings by altering the animals' cognitive, emotional, and physiological state during psychedelic exposure.

Environmental enrichment and communal housing. Environmental enrichment provides animals with complex physical, sensory, and social stimulation that better meets species-specific needs, thereby reducing stereotyped behaviours, improving welfare, and allowing animals to express more naturalistic behavioural repertoires. Enrichment has been shown to reveal richer phenotypes without increasing data variability (26–29), while at the same time reducing morbidity and mortality, compared to standard laboratory housing (30). Notably, environmental enrichment alters psychedelic-induced brain activity (31), and is a prerequisite for cognitive improvements following DMT exposure in ageing mice (32). Home cage monitoring in enriched environments can thus capture temporal patterns, social behaviours, and spontaneous activities of animals that improve translational relevance (33, 34). In our analysis, only 11 of 106 studies reported providing enriched home cages, while 95 studies either explicitly stated no enrichment or did not state this information (Figure 1).

In addition to physical enrichment, whether rodents are housed individually or in groups has profound effects on their well-being. Social isolation is a significant stressor that produces anxiety- and depression-like behaviour, cognitive deficits including impaired memory and social cognition, and altered immune and metabolic function (30, 35, 36). As such, individual housing in psychedelic experiments is highly likely to create confounds that may mask or distort experimental effects. Group housing can reduce such adverse effects by providing species-appropriate social contact, though the magnitude of isolation effects varies with strain, sex, and duration (37). In our analysis, 65 studies housed animals in groups (2-6 per cage), while 21 reported individual housing, and 20 studies did not specify housing conditions. Together, these findings indicate that impoverished, solitary housing conditions in some studies may severely curtail the therapeutic mechanisms of psychedelics.

Handling and habituation protocols. Handling technique and the extent of habituation to human contact profoundly impact rodent stress levels and behaviour. For example, conventional tail handling induces an anxiety-like state that changes how animals perceive and respond to rewards (38), while proper handling protocols markedly reduce stress responses and variability in behavioural tests (39–41). In our analysis, handling was reported in only 25 studies, whereas 81 studies did not provide this information (Figure 1).

Similarly, familiarization with the test arena aims to reduce novelty-induced stress and anxiety, allowing researchers to measure experimental effects rather than stress confounds. Brief arena familiarization has been shown to increase stimulus investigation and improve habituation–dishabituation performance in mice, with effects most pronounced in more anxious animals (40). Repeated exposure to test environments reduces novelty-induced anxiety and improves the reliability of exploratory behaviour measures (42), thereby enhancing statistical power and reproducibility. In our analysis, familiarization to the experimental setup was included in 55 studies, while 36 did not incorporate a habituation period, and 15 studies did not mention whether habituation was performed (Fig-

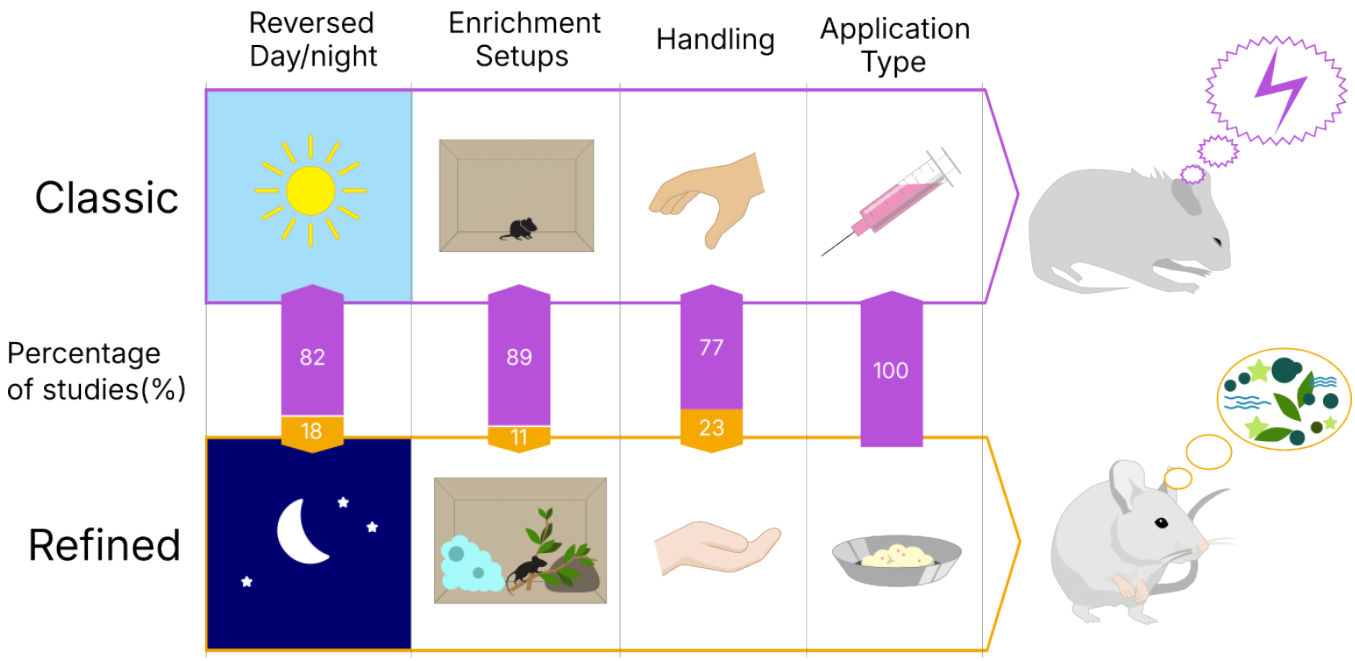

Fig. 1. Comparison of classic versus refined experimental practices in psychedelic animal research. Based on our systematic review of 106 rodent studies (2019-2024), the figure contrasts prevalent 'Classic' practices (purple) with recommended 'Refined' practices (orange) across four key parameters: circadian alignment (reversed day/night cycle), environmental enrichment and communal housing, handling and habituation protocols, and drug application method. Percentages for 'Classic' practices represent studies where the refined practice was either not implemented or not reported. Classic practices create stressed experimental conditions, while refined practices promote natural behavioural states (depicted by calm mouse in enriched setting).

ure 1). Given that familiarity with an environment has been shown to be a defining factor in shaping acute psychedelic responses in rodents (43), a lack of habituation may introduce substantial variability by conflating novelty-induced stress with psychedelic effects.

Drug administration (Figure 1). The route and method of drug administration represent an often overlooked welfare consideration that directly impacts the stress levels with which animals enter psychedelic experiences. Restraint, which is required for intraperitoneal injection, subcutaneous injection, and oral gavage, is itself a standard method to experimentally induce stress in rodents (44, 45). Evidence demonstrates that these routine administration procedures trigger substantial physiological stress responses, including elevated heart rate, increased body temperature, and raised corticosterone levels that can persist for several hours (46–48). In contrast, voluntary oral administration methods using palatable vehicles have been developed to minimize such stress, producing lower corticosterone levels and more stable cardiovascular responses (48, 49).

In our analysis, the vast majority of psychedelic studies relied on injection methods (Figure 1), with intraperitoneal (i.p.) administration accounting for 75% of applications, followed by subcutaneous (s.c.) at 13.8%, and oral gavage (p.o.) at 6.9% (Supplementary Fig. S3). Notably, despite the availability of voluntary oral administration methods that could minimize handling-related stress and better approximate a human clinical context, this approach appears to be entirely absent from the psychedelic literature. The predominant use of stressful administration methods raises the question: how can we expect to model the therapeutic effects of psychedelics when animals experience drug onset in a state of acute anxiety, precisely the condition known to predict poor outcomes in human patients?

Given that clinical psychedelic therapy depends on creating supportive, low-anxiety contexts to achieve positive therapeutic outcomes, the widespread neglect of analogous welfare practices in preclinical animal research (including environmental enrichment, stress reduction, active-phase testing, and careful handling) may compromise our ability to model and understand the neurobiological mechanisms underlying the therapeutic effects of psychedelics.

One recent clue that the therapeutic mechanisms of psychedelics may indeed be somewhat 'lost in translation' comes from a large-scale, multi-institutional study testing the effects of psilocybin using approximately 200 mice per experiment across five independent laboratories (50). Despite strong statistical power and transparent reporting, the study failed to find replicable therapeutic effects of psilocybin 24 hours post-administration. Specifically, psilocybin neither reduced behavioural markers of anxiety or depression, nor did it boost fear extinction or social reward learning. The only replicable effects were acute, including decreased fear expression and increases in anxiety and avoidance behaviours during drug administration.

While these results may point towards a low clinical utility of psilocybin and/or a strong divergence in the effects of psilocybin on humans and rodents, another possibility is that the observed effects were strongly shaped by experimental context: Like most studies surveyed in our analysis, (50) did not include environmental enrichment, handled animals by scruffing, administered psilocybin via intraperitoneal injection,

and conducted 80% of their experiments during the animals' inactive circadian phase.

Together, these aversive context factors may have had a sufficiently strong impact to counteract therapeutic mechanisms that might be engaged by psilocybin under different circumstances. This possibility also tallies with the study's finding that animals' anxiety increased consistently during drug administration — an effect one would expect to find in "bad trips" in a human context. These possible interpretations underscore the notion that particularly in psychedelic research, welfare practices are not peripheral considerations, but rather essential experimental parameters that determine the success of preclinical studies as a translatable model of therapeutic processes triggered by psychedelics in humans.

Tracking experiential dynamics

In humans, psychedelic substances induce a multitude of subjective experiences ranging from simple sensory alterations such as visual hallucinations and audiovisual synaesthesia, to complex cognitive changes such as disembodiment or impaired cognitive control. Perhaps most significantly, psychedelics can induce strong emotional responses such as feelings of catharsis and awe, as well as spiritual or mystical experiences, including feelings of unity and transcendence of space and time (51). Human studies have revealed that the subjective quality of acute psychedelic states predicts long-term therapeutic outcomes (52–54). Specifically, participants that report experiencing mystical or meaningful experiences during their sessions often achieve better long-term outcomes such as a reduction in depressive symptoms (15, 55), while participants who report aversive or anxious experiences may derive less benefit (56).

This raises a challenge for translational research: we cannot access the subjective experiences of animals through verbal report, but this does not mean that animals lack rich experiential states during psychedelic exposure. On the contrary, behavioural observations across species suggest that their subjective experiences may be noticeably altered. Cats under the influence of psychedelics grasp at the air with their paws, visually track objects not present in the environment, and pounce toward empty spaces (57, 58). Similarly, rhesus monkeys show "tracking" behaviour of invisible objects after hallucinogen administration (59). Most compellingly, recent work has directly demonstrated parallel visual distortions in humans and rats exposed to psilocybin using an identical behavioural paradigm (19). These converging observations indicate that animals are not merely exhibiting pharmacologically induced motor dysfunctions, but rather appear to respond to altered perceptual states that shape how they interact with their environment.

The problem, therefore, is not that animals necessarily lack subjective experiences during psychedelic exposure, but rather that current animal studies have not managed to characterize these experiential dynamics adequately. Most preclinical psychedelic research relies on isolated behavioural markers such as head twitches, total amount of locomotion, or brief snapshots of social interaction—measured at single time points or in highly constrained test conditions. This reductionist approach, while maximizing experimental control, may compromise translational validity (60–63). The head twitch response exemplifies this problem: while it shows remarkable predictive validity for identifying psychedelic compounds (64), it lacks face validity to any aspect of human phenomenology, it tells us little about the quality of the animal's experiential state, for instance whether perceptual changes it may be experiencing are aversive or pleasant. The lack of valid, standardized approaches for characterizing acute experiential states has for instance made it difficult to determine whether the same compound produces anxiolytic or anxiogenic effects, with conflicting outcomes likely reflecting contextual factors that alter the animal's overall experiential state (65).

To address this gap, we propose that animal research must move beyond simple behavioural markers toward comprehensive characterisation of experiential dynamics during psychedelic exposure. While we cannot directly measure subjective experience in animals, comprehensively tracking a multitude of behavioural components — such as altered sensory processing, changes in exploration-avoidance balance, social behaviour modifications, and temporal patterns of arousal and rest — allows us to characterize what constitutes a "psychedelic state" in animals and how different qualities of this state might predict downstream outcomes (61). Following the framework proposed by (60) for improving translational validity in psychiatric research, we identify three features that must be considered to adequately capture psychedelic-induced experiential dynamics in animal models: behavioural complexity, environmental diversity and temporal dynamics (Figure 2).

Capturing behavioural complexity. Human subjective experiences under psychedelics are multidimensional, encompassing perceptual, emotional, cognitive, and social domains. Reducing animal behaviour to single metrics (e.g. number of head twitches) may miss the very aspects of behaviour that reflect translationally and therapeutically relevant experiential states. Advances in computational ethology—combining automated behavioural tracking, machine learning-based behavioural classification, and analysis of behavioural sequences—now enable comprehensive, multidimensional characterization of behaviour without requiring labour-intensive manual scoring (60, 61, 66). These computational approaches enable researchers to detect complex behaviours such as social approach and retreat, affiliative interactions, defensive responses, and their sequential organization. For example, rather than measuring total social interaction time, we might characterize the sequential structure of social behaviours (approach → investigation → withdrawal), the balance between affiliative and defensive responses, the flexibility versus predictability of behavioural transitions, accompanying vocalizations, and how these patterns evolve over the course of psychedelic exposure. Recent computational approaches further demonstrate the power of behavioural characterization in extracting the complexity of underlying experiential states. For instance, machine-learning analysis of facial expressions in mice can reverse-engineer emotional states from

micro-expressions invisible to human observers (67), while ultrasonic vocalization analysis reveals that superficially similar behaviours can have opposite emotional valences (68). Such comprehensive behavioural characterization can capture measurable components of experience that may more faithfully reflect the experiential dynamics involved in the therapeutic effects of psychedelics in humans (61, 66).

Providing environmental diversity. In clinical settings, patients experience psychedelics in comfortable environments that allow for diverse behaviours including rest, movement, interaction with objects or music, and social connection with therapists. In contrast, most animal studies confine subjects to barren test environments that permit only a limited behavioural repertoire. This environmental impoverishment restricts the range of behaviours animals can express, potentially masking experiential dynamics that would be evident in more naturalistic settings (62, 63). For example, in a semi-naturalistic setting called the Visible Burrow System, mice clustered into 'stress-responsive' and 'stress non-responsive' phenotypes — a distinction that did not emerge in more confined settings (69). Similarly, psilocybin's anxiolytic effects (quantified by the elevated plus maze task) only emerged when rats received repeated exposure to novel environments during the weeks following psilocybin administration (70). These findings suggest that beneficial versus detrimental effects of psychedelics — and the mechanisms that produce them — may only be tractable when animals are studied in sufficiently complex environments that enable a diverse behavioural repertoire (60, 66).

Recording temporal dynamics. Human psychedelic experiences unfold over hours, with distinct phases including onset, peak effects, and gradual return to baseline — each associated with different experiential qualities. In contrast, the majority of animal studies measure behaviour in brief snapshots, e.g. by applying a brief open-field test. Such measurements by nature cannot reflect how behavioural states evolve across the time course of psychedelic exposure, whether they transition between distinct phases, and how these in turn might predict later outcomes. Moreover, fragmenting behavioural readouts e.g. by moving animals between test apparatuses or repeatedly handling them for serial testing may itself disrupt the natural evolution of psychedelic states. Long, continuous, and non-invasive behavioural monitoring throughout the psychedelic experience is essential to characterize how behavioural states evolve spontaneously over time, identify critical transition points, and detect temporal patterns that may predict therapeutic long-term effects (60, 66).

Our analysis of current psychedelic research in rodents highlights that most studies fall short of these recommendations (Figure 2). However, a small number of studies have begun to adopt more comprehensive approaches, demonstrating the feasibility and value of time-resolved recordings in enriched environments with improved behavioural characterization (71, 72). These pioneering efforts point toward a future where animal models can more faithfully capture the experiential dynamics that appear critical for therapeutic outcomes in humans.

Understanding psychedelic action in context

Individual differences in treatment response. Clinical outcomes in psychedelic therapy are characterized by substantial individual variation: while some patients experience intense mystical experiences and lasting therapeutic benefits, others experience psychologically distressing sensations and minimal therapeutic responses or even adverse effects (56). For instance, in psilocybin trials for treatment-resistant depression, therapeutic success rates typically range from 50-70% (4, 5). Multiple sources of variation could contribute to individual differences in psychedelic response, including genetic factors (73, 74), psychological factors such as personality traits (14, 75, 76), and set and setting (14, 77). Understanding this heterogeneity represents a major challenge for bringing psychedelic therapy into safe and effective clinical practice, and preclinical research can play a crucial role in tackling it. This approach is particularly promising because even mice raised under standardized conditions show substantial individual variation in behaviour and brain structure, providing a translationally valid target for individualized outcome prediction (78, 79). While perhaps surprising, this variation is readily understood when considering that early-life contingencies can generate self-reinforcing individual differences, which in turn become amplified through competitive social feedback, pushing genetically identical individuals onto divergent life trajectories (80).

Despite their ubiquity, inter-individual differences have been largely neglected by psychedelic research in animals, which has predominantly focused on group-level effects rather than tracking individual animals over time. As such, individual differences in behavioural or neural responses are rarely systematically characterized, and when observed, they are typically attributed to measurement error rather than recognized as potentially reflecting the same response heterogeneity seen in humans.

To address this gap, we must track how specific individuals behave from baseline through acute psychedelic exposure and into the weeks or months following treatment. Longitudinal designs in this vein allow us to ask central questions such as: How do baseline characteristics predict which animals will enter different acute experiential states, and how does this predict subsequent behavioural task performance? In human research, this approach has proven essential: studies tracking individuals across multiple time points have revealed that baseline brain network organization predicts treatment response (81), that changes in default mode network connectivity during acute psychedelic states correlate with symptom improvements weeks later (15, 82), and that individual differences in acute experiences mediate long-term outcomes (15). Yet in animal research, most studies employ between-subjects designs, preventing direct tracking of individual trajectories and thereby making it impossible to identify mechanisms and predictors of heterogenous treatment responses.

The social dimension of psychedelic therapy. Psychiatric disorders such as depression, anxiety, PTSD, and addiction are all essentially social in their manifestation and impact.

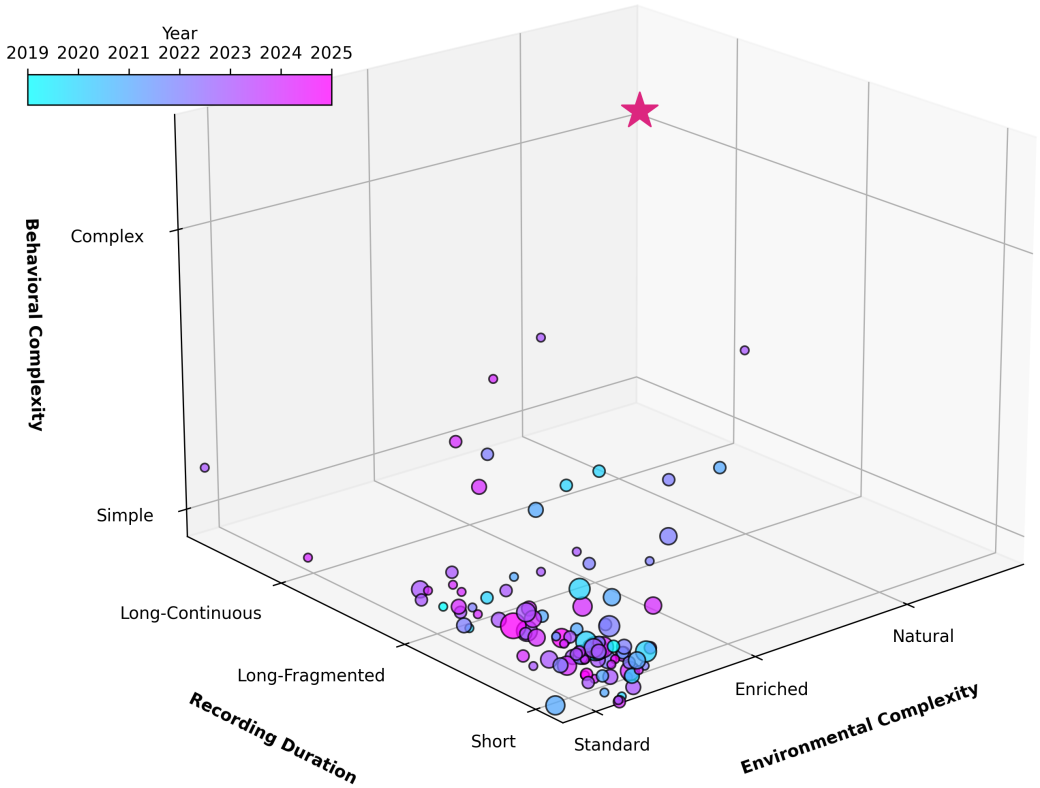

Fig. 2. Mapping behavioural assays in rodent psychedelic research. Each point represents one of 106 reviewed studies, positioned in three-dimensional space according to recording duration (x-axis: from brief single-session tests to extended continuous monitoring), environmental complexity (y-axis: from barren test apparatus to semi-naturalistic habitats), and behavioural complexity (z-axis: from single metrics like head twitches to multidimensional behavioural characterization). For a detailed description of the calculation, see the Supplementary Methods and Figures. Point size reflects the number of distinct behavioural assays employed within each study, while point colour indicates publication year. The pink star marks an aspirational direction: comprehensive, continuous behavioural monitoring in naturalistic environments—the approach most likely to capture therapeutically relevant experiential dynamics. See Supplementary Methods for detailed scoring criteria.

They disrupt social relationships, are exacerbated by social stress and isolation (83, 84), and often improve with social support and connection (85). Emerging evidence suggests that psychedelic therapy may exert therapeutic effects partly through improvements in social functioning: patients report enhanced feelings of connectedness, reduced social anxiety, increased empathy, and improved relationship quality following psychedelic experiences (86). Specifically, psilocybin reduces neural responses to social exclusion (87), enhances emotional empathy and prosocial behaviour (88, 89), improves social adaptation during interpersonal feedback (90), and increases feelings of trust and closeness to others (89). What's more, one of the central predictors of psychedelic therapy outcomes is the social bond formed with the supporting therapist(s) (12, 13), further highlighting that the therapeutic benefits of psychedelics are essentially social in nature. These findings suggest that understanding psychedelic mechanisms requires studying not just isolated individuals, but individuals embedded within a social context — how they navigate social hierarchies, form affiliations, respond to social stress, and how their position within social networks shifts over time.

Despite the deeply social nature of both psychiatric disorders and psychedelic therapy, preclinical psychedelic research has largely studied individual animals in isolation. This approach overlooks the possibility that psychedelics may exert therapeutic effects partly by altering how individuals interact with others. Recent methodological advances make it feasible to address this gap: automated behavioural tracking can now characterize social interactions in groups of animals over extended periods (91–93), social network analysis can reveal how psychedelic treatment alters an individual's position within a social hierarchy (94, 95), and wireless neural recording systems enable brain activity monitoring during naturalistic social behaviours (96, 97). Such approaches could reveal whether psychedelics alter social approach-avoidance behaviours, modify responses to social stress, change patterns of affiliative interaction, or shift an individual's dominance status. Moreover, studying individuals within their social context may be essential for capturing clinically relevant predictors, such as differing social positions, or adherence to distinct behavioural phenotypes (e.g., stress-responsive versus stress-resilient) (60). Given that social and empathy deficits

characterize treatment-resistant depression (84) and that improved connectedness mediates therapeutic outcomes (12, 98), animal models that fail to take social functioning into account may miss the very mechanisms most relevant to clinical translation.

Long-term persistence and temporal dynamics. One of the most remarkable features of psychedelic therapy is the persistence of therapeutic effects long after acute effects have subsided. In clinical trials, single or double dosing sessions produce symptom improvements that can last for months or even years (4, 5). This temporal profile — brief intervention, lasting change — implies that psychedelics rapidly initiate neurobiological processes that continue to unfold long after the drug has been metabolized.

Animal research has made substantial progress in identifying candidate mechanisms for these lasting effects, particularly focusing on neuroplasticity-related dynamics such as increased dendritic spine density, enhanced synaptic plasticity, and structural remodelling of cortical circuits (99–102). Some studies have achieved commendable longitudinal follow-ups, with the longest extending to approximately one month post-treatment (99, 103, 104)—a substantial commitment given the practical challenges of sustained monitoring in animal research.

Yet here lies a largely untapped opportunity unique to preclinical models: in humans, ethical and practical constraints limit our ability to study individuals for extended periods, whereas animal models allow us to track the same individuals across their entire lifespan—from early development through adulthood and into old age. This capacity for lifelong monitoring represents a profound advantage rather than merely a gap to fill. While human therapeutic effects persist for months or years, we can directly observe how psychedelic-induced changes unfold across developmental transitions, ageing processes, and shifting social contexts that would be impossible to capture in clinical trials. Moreover, behavioural assessments in animal studies typically occur at discrete time points rather than tracking phenotypic changes longitudinally in the same individuals (103, 105), and social behaviour dynamics remain largely uncharacterized despite their documented importance in human therapeutic outcomes (106).

Long-term longitudinal designs within a social context are essential to address this gap. Such approaches would allow us to identify early neural, behavioural, and social predictors of lasting change, to characterize the temporal evolution of both individual circuit reorganization and behavioural and social shifts beyond the initial days, and to link transient pharmacological effects to sustained therapeutic mechanisms. Moreover, by combining continuous behavioural tracking of individuals within social groups with repeated neural recordings, we could directly test mechanistic hypotheses about how acute circuit perturbations translate into the persistent changes in brain function, individual behaviour, and social functioning that characterize therapeutic response in humans.

Concluding Remarks

Our analysis identifies three interconnected domains where preclinical psychedelic research diverges from the conditions that determine the therapeutic success of psychedelics in humans, each representing both a current limitation and an opportunity for methodological advancement.

Set and setting: most animal studies employ stress-inducing conditions: barren housing, inactive-phase testing, forceful handling, and injection-based administration. These approaches fundamentally diverge from the supportive, low-anxiety contexts essential for positive therapeutic outcomes in humans. Adopting welfare-oriented practices such as environmental enrichment, communal housing, gentle handling, and circadian-aligned testing would create experimental conditions more likely to engage the same neurobiological mechanisms underlying human psychedelic therapy.

Experiential dynamics: current behavioral assays typically capture isolated markers at discrete time points rather than the multidimensional, temporally evolving states that predict therapeutic outcomes. Advances in computational ethology now enable comprehensive behavioral characterization in environmentally complex settings, offering a path toward capturing the richness of psychedelic-induced experiential states.

Individual and social context: while treatment response heterogeneity and social functioning are central to psychedelic therapy, most animal studies use group-level analyses of isolated individuals, precluding investigation of individual trajectories and social dynamics.

Together, these considerations point toward a fundamental reorientation: from brief, cross-sectional testing of stressed, isolated animals toward longitudinal tracking of individuals within enriched social environments. Neuroscience now holds the tools to meet this challenge, from complex analysis of naturalistic behaviours (107–109) to chronic neuronal recordings (96, 110) to long-term tracking of group dynamics (80, 95, 111).

When approached in this way, animal models offer unique insights, including the capacity for lifelong monitoring across developmental stages impossible to achieve in human studies, as well as the connection of dynamics across the levels of receptors, systems and behavior. By embracing these opportunities, preclinical research can move beyond demonstrating that psychedelics produce overall effects in animals towards understanding the neuronal, contextual, experiential, and individual factors that determine whether those effects translate into lasting therapeutic change.

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Supplementary Methods and Figures

We comprehensively reviewed articles that report the effects of psychedelics on rodent behaviour identified by a systematic search of the literature published in the last 5 years, with a date cutoff on the 28th of January, 2025. We used the following search prompt on PubMed for an initial list of studies:

```
(psychedelics[title/abstract] OR
 psilocybin[title/abstract] OR
 "lysergic acid diethylamide"[title/abstract])
AND
(mouse[title/abstract] OR mice[title/abstract] OR
 rat[title/abstract] OR rats[title/abstract])
```

This yielded 227 results from which we removed reviews, human clinical trials, pharmacological studies not including behavioural experiments, duplicate studies (preprint and article) and corrections. Of the selected studies, 13 were unaccessible due to being behind a paywall and therefore excluded, resulting in a total of 106 studies included in the review (See Figure S1).

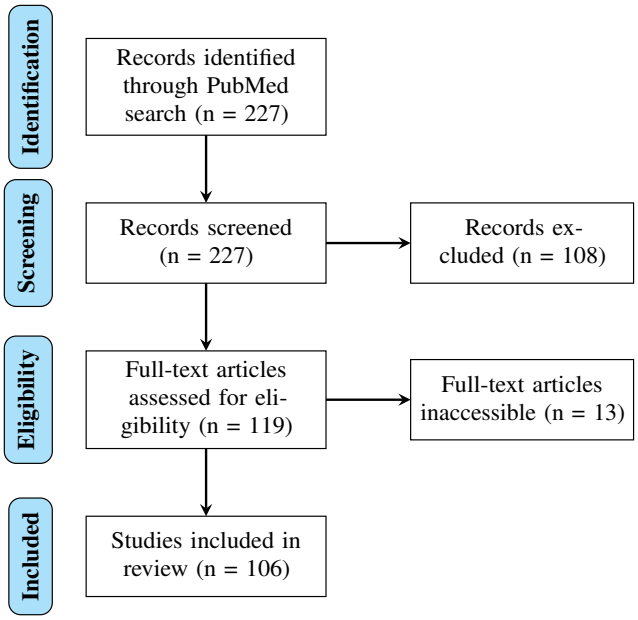

Fig. S1. PRISMA flow diagram of the study selection process.

Behavioural Assay Characterization. For each study, we extracted information about the behavioural assays used, including recording duration, environmental context, and behavioural complexity. To systematically compare experimental approaches across studies, we developed three scoring dimensions, each scaled from 0 to 15:

Recording Duration Score. Studies were first categorized as short (single brief test session), prolonged-fragmented (multiple test sessions across days), or long-continuous (extended continuous recording). For short recordings, scores ranged from 0-5, scaled by recording length relative to a 12-hour day. For prolonged-fragmented recordings, scores ranged from 5-10, scaled by total recording time (recording days × minutes per session). For long-continuous recordings, scores ranged from 10-15, scaled by the number of continuous recording days.

Behavioural Complexity Score. Assays were categorized as simple (measuring single behavioural metrics such as total locomotion or head twitches) or complex (measuring multiple behavioural dimensions, sequential patterns, or ethologically relevant behaviours). Simple assays received scores from 0-7.5, while complex assays received scores from 7.5-15, with further scaling based on the number of distinct behavioural measures captured.

Environmental Complexity Score. Testing environments were categorized as standard (barren test apparatus such as open field or elevated plus maze), enriched (home cage or arena with nesting material, shelters, or enrichment objects), or naturalistic (semi-natural environments approximating species-typical habitats). Standard environments received scores from 0-5, enriched environments from 5-10, and naturalistic environments from 10-15, with further scaling based on the diversity of environmental features present.

For studies reporting multiple behavioural assays, mean scores across assays were calculated to generate a single study-level score for each dimension. The three-dimensional distribution of studies was visualized using these scores, with point size representing the number of assays per study and color indicating publication year.

Fig. S2. Systematic analysis of experimental conditions in psychedelic animal studies. Literature review for all studies using rodents in psychedelic research, from 2019 till 2024. Status indicates whether studies included specific practices (yes: green, no: pink). Grey bars represent studies where this information was not reported in the publication, preventing assessment of whether the practice was implemented.

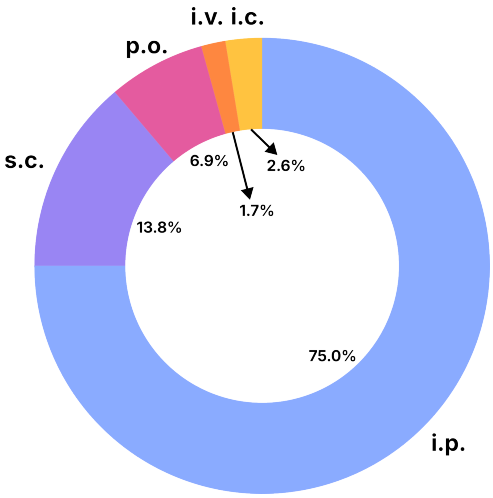

Fig. S3. Distribution of application types used in the reviewed studies. Intraperitoneal injections (i.p.) account for 75% of the application methods, subcutaneous injections (s.c.) for 13.8%, oral gavage (p.o.) represents 6.9%, while intracranial (i.c.) and intravenous (i.v.) were used in 2.6% and 1.7% of cases, respectively.