REVIEW ARTICLE

Psychedelic studies in nonhuman primates: Past and future

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Studies of serotonergic or 'classic' psychedelics in nonhuman primates (NHPs) have provided valuable information about the drugs' effects on the brain and behavior in closely related species to humans. Psychedelics induce characteristic changes to both spontaneous and operant behaviors in NHPs, though variability exists in the different effects reported by different studies; this variability could be due to factors like differences across drugs, differences in dose ranges across studies, and inter-individual variability in drug responsiveness. Several effects of psychedelics in NHPs mirror those in humans, including development of tolerance to psychedelic effects and low abuse liability, though evidence is mixed on whether psychedelics cause visual hallucinations in NHPs. NHP studies have also examined psychedelic mechanisms of action, supporting and connecting existing findings from human and rodent studies. Here we review the knowledge gained from psychedelic research in NHPs encompassing multiple psychedelic compounds in several NHP species. We conclude by highlighting NHPs' potential to serve as preclinical models of psychedelic effects on psychiatric conditions and suggesting several directions for future research to ensure the accuracy and effectiveness of an NHP psychedelic model.

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INTRODUCTION AND CHARACTERISTIC PSYCHEDELIC EFFECTS

Serotonergic psychedelics are a diverse family of compounds with a wealth of complex and dramatic effects on behavior, ranging from intense acute changes to perception and cognition, to seemingly promising therapeutic potential in treating a variety of psychiatric disorders [1–5]. Much of the research that has been conducted with psychedelics has focused on their effects in humans. However, a subset of psychedelic work has examined the drugs' effects in nonhuman primates (NHPs). Studying a drug in NHPs can provide invaluable information about aspects like the drug's safety profile and mechanisms of action, and NHPs can serve as excellent preclinical models of drug effects [6, 7]. This review aims to characterize and summarize research examining the effects of psychedelics on NHP behavior, with a focus on 'classic' psychedelics (e.g., those that act primarily as agonists of the serotonin 2A receptor, or 5-HT2AR; although compounds like MDMA and ketamine share some similarities with classic psychedelics in terms of their effects [8, 9], they do not act primarily as 5-HT2AR agonists [10, 11]). Specifically, this review will primarily cover studies of psilocybin (the main psychoactive component of hallucinogenic mushrooms), lysergic acid diethylamide (LSD, a semi-synthetic psychedelic discovered in the 1930s), dimethyltryptamine (DMT, a major component of ayahuasca), and mescaline (the active ingredient of the peyote cactus and similar species) (Fig. 1). We first review work focusing on the effects of psychedelics on spontaneous (e.g., non-task related) behavior in NHPs, followed by consideration of potential parallels to the subjective effects of psychedelics in humans. We then discuss psychedelics' relative lack of reinforcing properties and abuse liability, followed by coverage of some possible mechanisms of action. Finally, we conclude by emphasizing the role of NHP studies in preclinical models of psychedelic effects and suggesting several directions for future research. To see the NHP species included in this review, see Fig. 2.

Characteristic behavioral changes induced by psychedelics

Acutely, psychedelics appear to cause several characteristic stereotyped motor behaviors in NHPs. Spasmodic movements of the extremities, referred to as 'limb jerks,' are one of the most commonly recorded metrics of psychedelic effects in NHPs. Stump-tailed macaques (*Macaca arctoides*) displayed limb jerks after individual injections of LSD, DMT, psilocybin, and mescaline [12–14]. Similar movements were reported in studies of LSD and DMT in chimpanzees (*Pan troglodytes*) [15, 16], and in studies of LSD in rhesus macaques (*Macaca mulatta*) [17].

LSD, DMT, and mescaline all cause body shakes in NHPs, though reports are split as to whether these movements more closely resemble 'wet-dog shakes' (rapid back-and-forth shaking that starts at the head and travels down the body, similar to a dog shaking off water) [12–14] or spasmodic jerking of the body [17–20]. While psilocybin induced head twitching in one study of rhesus macaques [21], it has never been reported to cause the characteristic body shakes induced by other psychedelics, and in fact failed to produce this effect in a study of stump-tailed macaques [12]. Psilocybin, along with DMT and LSD, has caused animals to adopt atypical stereotyped postures, described by one study as 'bizarre' [17, 21]. No reports indicate that mescaline has similar postural effects. LSD and DMT additionally induce other

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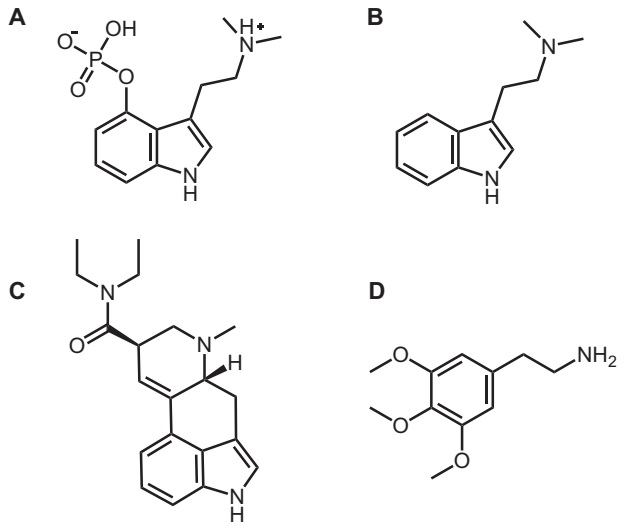

Fig. 1 Chemical structures of classic serotonergic psychedelics. **A** psilocybin ($C_{12}H_{17}N_2O_4P$); **B** DMT (N,N-dimethyltryptamine, $C_{12}H_{16}N_2$); **C** LSD (lysergic acid diethylamide, $C_{20}H_{25}N_3O$); **D** mescaline ($C_{11}H_{17}NO_3$).

stereotyped behaviors, including hand and head movements and rocking behavior [19]. Some of these stereotyped behaviors are reminiscent of motor behaviors seen in other species after administration of serotonergic psychedelics, such as limb flicking in cats [22, 23] or the head-twitch response (HTR) in mice. HTRs, which present as rapid back-and-forth movements of the head, correlate with 5-HT2AR stimulation and are the most commonly used metric of psychedelic effects in mouse studies [24–29].

Psychedelics also induce a variety of other effects in NHPs. Rhesus macaques showed decreases in self-grooming after administration of LSD and DMT [19], while studies of stump-tailed macaques reported decreases in both self- and social grooming [12, 14]. These decreases in grooming may be analogous to the abortive grooming observed in cats after LSD administration [23]. Some psychedelics induce characteristic facial behaviors, including particular patterns of mouth movements like chewing and licking. This 'oral syndrome' was first shown to be caused by mescaline [18], but has also been induced by LSD in rhesus macaques [17] and by psilocybin in Guinea baboons (*Papio papio*) [30]. It is noteworthy that none of these studies utilized oral drug administration, so this 'oral syndrome' is unlikely to have been caused by a reaction to the method of administration. Mescaline and LSD have additionally been shown to cause ptosis (drooping of the eyelids) in stump-tailed macaques [12]. A study of psilocybin in rhesus macaques, conversely, found that it did not cause ptosis after comparing it to ptosis-inducing drugs [31].

Effects of psychedelics on general activity and locomotion levels in NHPs can vary. Mescaline is the only psychedelic that appears to universally decrease activity levels, though some reports of LSD in stump-tailed macaques and psilocybin in baboons note decreased activity and increased resting behavior after administration [12, 14, 30]. Typically, however, LSD and psilocybin tend to induce patterns of differential activity levels, with locomotion increasing soon after drug administration and decreasing below baseline after a few hours, before the drug's acute effects wear off; this pattern was observed with LSD in chimpanzees [15], and with psilocybin in rhesus macaques [32]. By contrast, DMT has been found to generally increase locomotion and hyperactivity in rhesus macaques and chimpanzees, though the study of chimpanzees found that locomotion may decrease at high doses of DMT (4 mg/kg) [16, 19, 21]. DMT also has not been reported to cause ataxia or a loss of motor coordination, which have been induced by mescaline, LSD, and psilocybin in rhesus macaques [17, 20, 32], and by psilocybin in baboons [30].

Psychedelics can also have impacts beyond simple motor behaviors in NHPs. Characteristic patterns of visual scanning have been noted after administration of LSD, DMT, and psilocybin in both rhesus and stump-tailed macaques [12, 13, 17, 21], and after mescaline administration in rhesus macaques [33]. This behavior can include fixating on points with no external stimuli [33]. Fear grimaces and other fear responses have been evoked by LSD and mescaline in rhesus macaques [19, 20], and by LSD in chimpanzees; LSD also uniquely elicited aggressive behaviors in chimpanzees [15]. One study of DMT in chimpanzees observed transient fearful and threatening gestures immediately after drug administration, but concluded that this was likely due to the nature of administration; the study took place in a wildlife park where animals did not have regular human contact, so DMT and control injections were administered using a dart gun, which the animals may have found startling or aversive [16]. Additionally, increased rates of yawning have been reported following administrations of LSD and DMT in rhesus macaques [19], and of psilocybin in baboons [30]. Yawning can serve as a threatening gesture for NHPs in some contexts, but it is unclear from the context of the studies whether or not this was the case [34].

Finally, a few studies have examined psychedelics' effects on autonomic measures in NHPs. Piloerection and dilated pupils are induced by mescaline and psilocybin in rhesus macaques [20, 32] and by LSD in chimpanzees [15]. Mescaline has also been shown to cause salivation and vascular flushing in rhesus macaques [20], while LSD additionally caused irregular breathing in rhesus macaques and chimpanzees [15, 17]. One study of mescaline found that it caused similar changes to respiration rates in rhesus macaques [20], though these results are contradicted by another report that mescaline caused little change to heart rate and respiration in macaques [33]. To the best of our knowledge, there is little data on DMT's autonomic effects in NHPs. In general, the autonomic effects of psychedelics in NHPs are consistent with those reported in humans, which include pupil dilation and increases in heart rate and blood pressure [35–37]. For an overview of dose-response relationships of psychedelics' acute behavioral effects in NHPs, see Table 1.

Variability in drug effects

While some behavioral effects (limb jerks, body shakes, decreased grooming rates) appear to be relatively consistent across most or all of the psychedelics reviewed here, there is generally substantial variability in the effects induced both by different drugs and in different studies of the same drug. This variability could be due to several factors.

Although all four psychedelics show notable similarities in terms of their behavioral effects and mechanisms of action, they also have a number of key differences. In particular, although all psychedelics act primarily on the 5-HT2AR, their binding affinity for other receptors is complex and can differ between drugs. Psychedelics bind (indirectly, in the case of psilocybin; its primary psychoactive metabolite, psilocin, binds directly to receptors [38]) with varying affinity to other serotonin receptor subtypes, including 5-HT1A, 5-HT2B, 5-HT2C, 5-HT6, and 5-HT7 receptors. LSD shows high affinity for both α1 and α2-adrenergic receptors. DMT also binds to α1-adrenergic receptors, though LSD's affinity for the receptor is higher than DMT's [39]. LSD additionally binds to dopamine receptor subtypes D1–D4, while psilocybin (via psilocin) and DMT show no significant affinity for dopamine receptors [40–43]. There is comparatively less data regarding mescaline's mechanisms of action, but some evidence suggests that it may bind to α2A-adrenergic receptors and some dopamine receptor subtypes, though with less affinity than LSD [44, 45]. Differences in binding profiles mean that different psychedelics

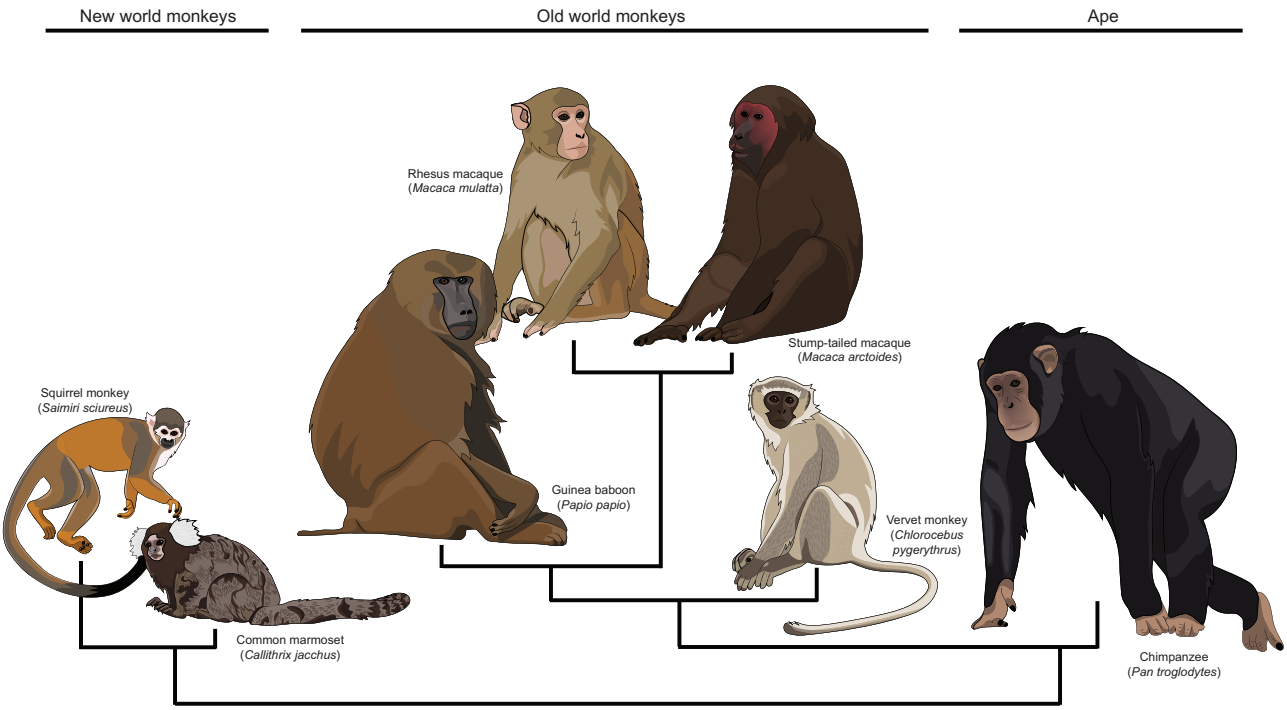

Fig. 2 NHP species utilized in psychedelic studies, organized in a phylogenetic tree.

may activate substantially different downstream mechanisms, which may explain some of the variability in behavioral effects.

Variability in effects could also be due to different ranges of doses. Across drugs, different dose ranges are employed because psychedelics differ in their potency, a phenomenon observed in humans and NHPs. LSD is the most potent and mescaline the least, with psilocybin and DMT falling in between. Human studies report that mescaline is approximately 30 times less potent than psilocybin, and up to 4900 times less potent than LSD [44, 46]. This relatively low potency is thought to be due to mescaline's low lipid solubility, making it difficult for mescaline to cross the blood-brain barrier (psilocybin also has low lipid solubility, but psilocin is more lipid soluble and able to cross the blood-brain barrier more easily) [40, 47–49]. Within a study, animals may be given different doses because of inter-individual variability in responsiveness to a psychedelic. Studies of operant behavioral performance in macaques, vervet monkeys (*Chlorocebus pygerythrus;* identified as *Cercopithecus aethiops* due to outdated classification), and squirrel monkeys (*Saimiri sciureus*) have found that a given dose of LSD can significantly impact performance in some animals while having little effect in others [50–53]. Individual squirrel monkeys also differed in the amount of time that it took for LSD-induced deficits in behavioral performance to resolve, with time frames ranging from two weeks to six months [53]. Inter-individual variability is also seen in human studies in domains ranging from behavioral effects to plasma concentrations of drug metabolites [38, 54], possibly due to genetic differences impacting the responses of 5-HT2ARs to psychedelic binding [55].

The variety in effects could also be due to differences in routes of administration. Intravenous and intramuscular administration are commonly chosen in NHP psychedelic studies, but other methods, including oral, subcutaneous, and intraperitoneal administration, have also been used. Route of administration can significantly impact pharmacokinetics, altering factors like the time course of drug absorption and a drug's bioavailability [56, 57]. Thus, the method of drug administration can substantially change the magnitude of a drug's effects; future work should aim to standardize factors like dosage and route of administration to obtain a more accurate understanding of psychedelics' behavioral profiles in NHPs.

Finally, the effects of psychedelics on NHP behavior may vary based on environmental context. One study of DMT examined the drug's effects in chimpanzees that lived free-range in a wildlife park [12]. Though the animals displayed several notable drug effects, including increased locomotion, they showed almost none of the characteristic psychedelic effects seen in most NHP studies. The authors speculated that, in laboratory environments, psychedelic-induced increases in arousal may be channeled into abnormal, stereotyped behaviors, while in this study, the chimpanzees' naturalistic habitats and social structures may have provided an outlet for the DMT-induced hyperactivity. Of particular interest, the animals showed none of the fearful reactions that have been seen in some NHP psychedelic studies, leading the authors to theorize that environmental setting may be able to mediate and attenuate aversive reactions to psychedelics in NHPs [12]. However, much more work is needed to determine the extent to which environmental context modulates the effects of psychedelics in NHPs, as well as the mechanisms underlying this modulation.

Tolerance to psychedelic effects

Human psychedelic studies indicate that repeated usage can lead to tolerance, or a decrease in an individual's reaction to a drug after repeated use [58, 59]. Tolerance has been similarly demonstrated for several psychedelic effects in NHPs. Stump-tailed macaques, when given daily doses of LSD, mescaline, or psilocybin, display tolerance to several characteristic psychedelic behaviors, including limb jerks and body shakes [12, 14]. Tolerance also develops to behavioral task performance. LSD-induced impairments in performance on several operant behavioral tasks were shown to attenuate over time with repeated administration in rhesus and stump-tailed macaques [52, 60]. Tolerance can persist even if psychedelics are not given daily: rhesus macaques showed tolerance to LSD's effects on an operant behavioral task even when administrations were separated by two weeks [52]. The exact time scale of tolerance in NHPs is unclear, though it appears

Table 1. Dose-response relationships for acute behavioral effects of psychedelics in NHPs.

Drug effect	Psilocybin	LSD	DMT	Mescaline
Limb jerks	0.4 mg/kg, IM [12]	0.01 mg/kg, IM [12–14]; 0.125–1 mg/kg, SC[a] [17]; 0.6 mg, oral [15]	0.5–4 mg/kg, IM [16]; 2 mg/kg, IM [12, 14]	17 mg/kg, IM [12, 14]
Body shakes	N/A	50 & 100 µg/kg, IM [19]; 0.01 mg/kg, IM [12–14]; 0.125–1 mg/kg, SC[a] [17]	1, 2, & 4 mg/kg, IM [12, 14, 19]	17 mg/kg, IM [12, 14]; 250 mg, IP [18, 142]; 10–130 mg/kg, IV[c] [20]
Stereotyped movements (other)	N/A	50 & 100 µg/kg, IM [19]	4 mg/kg [19]	N/A
Decreased grooming (self)	0.4 mg/kg, IM [12]	50 & 100 µg/kg, IM [19]; 0.01 mg/kg, IM [12]	1, 2, & 4 mg/kg, IM [12, 14, 19]	17 mg/kg, IM [12]
Decreased grooming (social)	0.4 mg/kg, IM [12]	0.01 mg/kg, IM [12]	2 mg/kg, IM [12, 14]	17 mg/kg, IM [12]
Oral effects	0.3 mg/kg, IV [30]	0.125–1 mg/kg, SC[a] [17]	N/A	250 mg, IP [18, 142]
Ptosis	N/A	0.01 mg/kg, IM [12]	N/A	17 mg/kg, IM [12]
Activity trend: increase -> decrease	2–4 mg/kg, IP [32]	0.6 mg, oral [15]	N/A	N/A
Decreased activity	0.3 mg/kg, IV [30]	0.01 mg/kg, IM [12, 14]	N/A	17 mg/kg, IM [12, 14]
Hyperactivity	0.03 µg/kg–0.01 mg/kg, IV[b] [21]	N/A	1 & 4 mg/kg, IM [19]; 0.3 µg/kg–0.01 mg/kg, IV[b] [21]	N/A
Visual scanning/tracking	0.4 mg/kg, IM [12]; 0.03 µg/kg–0.01 mg/kg, IV[b] [21]	0.01 mg/kg, IM [12]; 0.125–1 mg/kg, SC[a] [17]	1, 2, & 4 mg/kg, IM [12, 19]; 0.3 µg/kg–0.01 mg/kg, IV[b] [21]	20–100 mg/kg, IV, 20 & 40 mg, oral [33]
Odd body postures	0.03 µg/kg–0.01 mg/kg, IV[b] [21]	0.125–1 mg/kg, SC[a] [17]	0.3 µg/kg–0.01 mg/kg, IV[b] [21]	N/A
Ataxia/clumsiness	0.3 mg/kg, IV [30]; 2–4 mg/kg, IP [32]	0.125–1 mg/kg, SC[a] [17]	N/A	10–130 mg/kg, IV[c] [20]
Autonomic effects	2–4 mg/kg, IP [32]	0.125–1 mg/kg, SC[a] [17]; 0.6 mg, oral [15]	N/A	10–130 mg/kg, IV[c] [20]; 20–100 mg/kg, IV, 20 & 40 mg, oral [33]
Fear response	N/A	100 µg/kg, IM [19]; 0.125–1 mg/kg, SC[a] [17]; 0.6 mg, oral [15]	N/A[d]	10–130 mg/kg, IV[c] [20]
Aggression	N/A	0.125–1 mg/kg, SC[a] [17]; 0.6 mg, oral [15]	N/A[d]	N/A
Yawning	0.3 mg/kg, IV [30]	50 & 100 µg/kg, IM [19]	1 & 4 mg/kg, IM [19]	N/A

IM intramuscular, *IP* intraperitoneal[5], *IV* intravenous, *SC* subcutaneous.
[a]Effects noted to appear "at higher doses;" unclear which specific doses this refers to.
[b]Doses used in self-administration study; effects noted in sessions "when drug intake was high".
[c]Study examined effects up to 200 mg/kg, but 130 mg/kg was noted as the LD50 of mescaline.
[d]These effects were noted in one study [16], but thought to be due to method of administration so not counted here.
[e]This method of administration is atypical in NHP studies, but was used in one study of psilocybin in rhesus macaques [32].

to develop within about five days for both spontaneous and operant behaviors [12, 14, 60]; in humans, tolerance to LSD can decrease after only a few days of not taking the drug [58]. Different psychedelics can also show cross-tolerance (e.g., tolerance to the effects of one psychedelic can cause tolerance for the effects of another, without repeated administration of the second drug), likely due to psychedelics' shared mechanisms of action [46, 61]. Cross-tolerance is commonly reported for effects that show direct tolerance in one of the tested drugs: stump-tailed macaques given mescaline after two days of LSD administration showed lower rates of limb jerks and body shakes after both mescaline administration and the second LSD administration, compared to the first LSD administration [12], and human studies of mescaline and LSD [46] and psilocybin and LSD [61] report similar trends of both direct and cross-tolerance to the same drug effects.

DMT, unlike other psychedelics, does not reliably induce tolerance. Studies in stump-tailed macaques found either that repeated DMT administration did not cause tolerance [12], or that tolerance developed only to specific effects: in one study, macaques developed tolerance to DMT-induced hypervigilance, but not to limb jerks or body shakes [14]. A study in squirrel monkeys found no evidence of tolerance to DMT on a fixed ratio operant task, even after over a month of daily administration [62]. It is unclear what specific properties of DMT cause it to differ from other psychedelics' distinct patterns of tolerance induction; this difference may arise from the aforementioned differences in binding profiles across psychedelics.

DO PSYCHEDELIC DRUGS CAUSE VISUAL HALLUCINATIONS IN NHPS?

In humans, visual hallucinations are some of the most striking and well-known effects of psychedelics, and are typically assessed with self-report measures [47, 58, 59, 63, 64]. In NHPs, the question of whether psychedelics cause hallucinations is more complex. However, several studies have provided descriptions of NHPs, after being administered a psychedelic drug, seeming to react to a visual stimulus without any such stimulus being present.

In rhesus macaques, mescaline induces visual exploration behaviors – similar to those seen when a novel object was introduced – in response to no apparent stimulus. These behaviors were interpreted by experimenters as visual hallucinations [33]. Another study in rhesus macaques found that DMT, psilocybin and mescaline all caused visual scanning of the room as well as what the authors dubbed 'fly-catching' (quickly reaching for an empty point in space, as though attempting to grasp some invisible stimulus) [21]. Similar reaching behaviors were seen in macaques after LSD and DMT in another study [19]. These behaviors may be similar to the limb jerks identified in other studies, though descriptions of fly-catching [21] suggest that it is more purposeful than the aimless movements associated with limb jerks [12, 14], possibly indicating that it is a separate, visually-driven behavior. Some studies have gone so far as to build the assumption of hallucinatory effects into their designs: one study of the effects of mescaline in rhesus macaques and other species includes apparent hallucinations as a behavioral measure, presumably referring to a visual behavioral effect, though no specific definition is provided [20].

Some others in the field, however, remain less convinced that psychedelics induce visual hallucinations in NHPs. One study of the acute effects of LSD and DMT in rhesus macaques defined a list of several behaviors (including visual tracking) that the authors believed, if present, would indicate visual hallucinations. Though both drugs increased rates of visual tracking, the increases were neither significant nor consistent enough to suggest that the animals had been hallucinating. Instead, a potential alternative explanation was offered: that, in NHPs, psychedelics may shift attention from external stimuli (both real and hallucinated) to internally-generated stimuli. This explanation was proposed based on observations that macaques significantly decreased the amount of time they spent exploring their environment after psychedelic administration [19]. Support for this explanation may be found in reports of impaired operant behavioral performance after LSD administration in rhesus macaques [51, 52, 65, 66] and squirrel monkeys [53]: several of these studies [52, 53] hypothesized that LSD may impact attention, either by making animals more distractible or by shifting attention onto task-irrelevant stimuli. Support from human studies is mixed; while one study reported that psilocybin decreased participants' ability to shift attention to new targets from previously attended ones, a study of low doses of LSD found variable effects on attention, possibly including enhancements of sustained attention [67, 68].

Overall, evidence and opinions are mixed on whether psychedelics cause true visual hallucinations in NHPs. This question will likely remain unanswered unless it is addressed more directly: it is possible that visual hallucinations in NHPs could be examined with some sort of visual detection test applying a signal detection theory; similar procedures have been applied to detect hallucination-like percepts in mice and self-reported hallucinations in people [69]. If there is a significant increase in false alarm rate (responses indicating that a visual stimulus was detected when no stimulus was presented) after psychedelic administration, this could indicate that the animals are in fact hallucinating.

REINFORCING PROPERTIES AND ABUSE LIABILITY

A drug's ability to act as a reinforcer in animal models may correspond to its abuse liability in humans [70]. Psychedelics do not tend to be strong reinforcers in NHPs. One study assessed the reinforcing effects of a range of doses of psilocybin, DMT, and mescaline (psilocybin: 0.03 µg/kg–0.01 mg/kg/infusion; DMT: 0.3 µg/kg–0.01 mg/kg; mescaline: 0.3 µg/kg–0.1 mg/kg; see Table 1 for more information) by testing whether rhesus macaques would self-administer the drugs on an FR-30 schedule [21]. Mean rates of responding to all three drugs were low, though there was some irregularity to the animals' responses, and several occasionally responded at high rates to various doses of each drug. These high response rates were transient and did not conform to any identifiable pattern of responding. When psilocybin and DMT were retested at doses that had previously engendered significant reinforcement in select animals, response rates were notably lower and did not significantly rise again. The authors reported that the changes in self-administration behaviors across sessions did not resemble typical patterns of response extinction (in which initially high response rates gradually diminish over time). The lack of reliable reinforcing effects and overall low rates of self-administration support theories that psychedelics may either be weakly reinforcing or demonstrate a combination of reinforcing and aversive effects [21].

The latter conclusion is partially supported by data regarding the reinforcing effects of LSD in NHPs. A study in baboons trained to self-administer LSD (0.00032–0.032 mg/kg/injection) on an FR-160 schedule of reinforcement (initially trained with cocaine, a highly reinforcing drug) reported overall low rates of self-injection: in a daily access procedure, LSD and saline response rates rarely differed, and while rates of LSD self-injection were somewhat higher in an intermittent access procedure with discriminative stimuli (where LSD was only available for self-injection every six to ten days), they were still significantly lower than response rates for cocaine. Additionally, one animal never self-administered LSD at rates above saline responding [71]. In rhesus macaques, infusions of LSD have been shown to increase rates of avoidance behavior. Monkeys were trained to press a lever when a light turned on to avoid an aversive stimulus (initially a mild shock, which was replaced by automatic infusions of LSD once drug trials began)

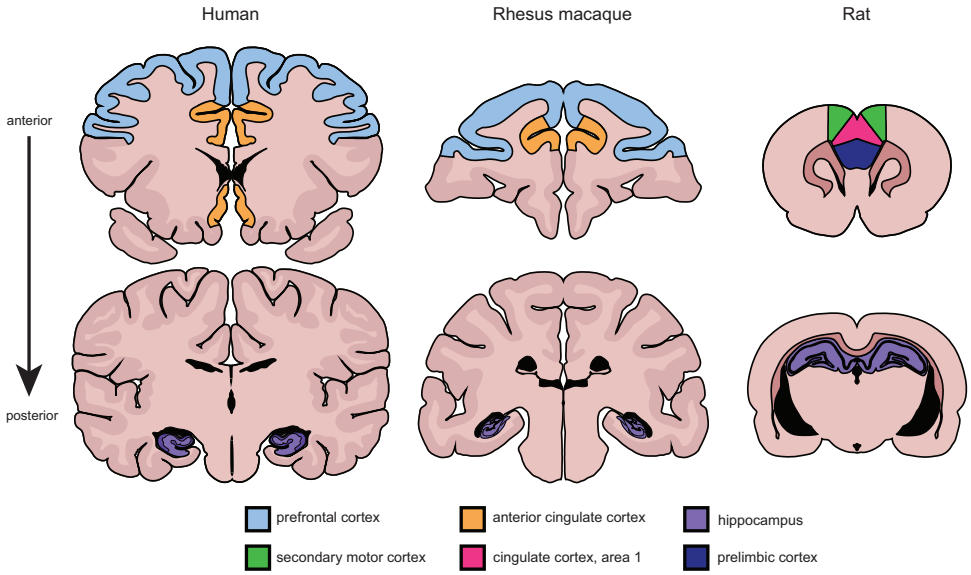

Fig. 3 Brain areas identified as areas of psychedelic action in humans, NHPs, and rodents. In the rat brain, secondary motor cortex and prelimbic cortex are identified as analogous to the human PFC, and cingulate cortex as analogous to the human ACC. Human brain sections referenced from the Allen Institute's modified Brodmann cortical atlas [148]; macaque brain sections referenced from Saleem & Logothetis [149]; rat brain sections referenced from Paxinos & Watson [150].

that followed the light. Rates of lever pressing were significantly higher in sessions where high doses of LSD (2.5 µg/kg) were administered, compared to saline, demonstrating the animals' motivation to avoid LSD injections [72]. Interestingly, given the rapid tolerance associated with many effects of LSD [52, 60], tolerance did not develop for this avoidance behavior. Regardless, it is clear that LSD is not a strong reinforcer, and may even be aversive [71, 72]. Although psilocybin, DMT, and mescaline do not appear to be fully aversive, it is possible that their weak, irregular reinforcing properties may stem partially from similar aversive effects [21, 72].

Overall, it appears that psychedelic drugs do not have strong reinforcing properties in NHPs, a conclusion mirrored by their low abuse liability in humans. Serotonergic psychedelics do not cause notable withdrawal symptoms, negating the need to take more of the drug to offset unpleasant physiological effects. The demonstration of tolerance to the effects of several serotonergic psychedelics in humans and NHPs [12, 14, 52] could raise the concern of individuals needing to increase dosage with each use, but tolerance tends to be abolished if an individual abstains from psychedelic usage for at least a few days after their last use. Daily usage is extremely uncommon; as a review of LSD use notes, psychedelics can have such intense subjective effects that individuals who use them naturally tend to space out their frequency of use, reducing the occurrence of tolerance [47, 58, 59, 63]. Thus, the reinforcing properties of psychedelic drugs appear to be low in both humans and NHPs. Indeed, psychedelics may even reduce the reinforcing properties of other drugs when co-administered. In rodents, psilocybin was shown to reduce heroin-seeking [73], and the psychedelic DOI was shown to reduce motivation to work for heroin, an effect that was blocked by a 5-HT2AR antagonist [74]. In rhesus macaques, contingent administration of the psychedelic DOM in combination with heroin reduced heroin self-administration rates [75]. Similarly, in clinical trials, psilocybin showed efficacy in treating alcohol use disorder [1] and promoting cessation of tobacco smoking [76].

BIOLOGICAL EFFECTS AND MECHANISMS OF ACTION

Though all classic serotonergic psychedelics act primarily as agonists at 5-HT2ARs, they enact a wealth of complex biological effects through various mechanisms of action, many of which are poorly understood. Compared to behavioral studies, there is a lack of research on psychedelics' neural effects and mechanisms of action in NHPs. In this section, we review existing neuroimaging and anatomical studies of psychedelic effects in NHPs, corroborating their findings with those from human studies. We also discuss select neural investigations of psychedelic effects in rodents, which could serve to guide future NHP psychedelic research. For an overview of brain areas identified as substrates of psychedelic action in studies of human, NHP, and rodent brains, see Fig. 3.

Existing neural studies in NHPs

Psychedelics' dramatic effects on behavior and perception tend to occur alongside, and perhaps as a result of, acute changes in neural activity. EEG studies of psychedelics in NHPs have found some consistent neural effects. In rhesus macaques, LSD and psilocybin have been reported to increase beta or higher frequency activity soon after administration [17, 32], while psilocybin also decreased alpha band activity [32]. These faster frequencies are then gradually replaced by slow wave activity over the course of the next several hours; one study noted that this trend corresponded to a decrease in movement and the appearance of drowsy facial expressions [17, 32]. In general, these activity patterns correlate with the movement trends (initial transient increases and later decreases in movement levels) observed in NHPs after administration of LSD and psilocybin [15, 32]. Psilocybin was reported to alter neural activity in the macaque neocortex and limbic regions, while LSD's effects were pronounced in the frontal cortex [17, 32]. EEG and MEG studies in humans have also reported characteristic neural effects of psychedelics. LSD [77, 78], DMT (via studies of ayahuasca) [79, 80], and psilocybin [81] all tend to reduce oscillatory power in neocortical regions and, in some studies [78, 81], the default mode network (DMN). Some studies find these reductions only in lower frequency bands like delta, theta, and alpha bands (perhaps similar to the reduction in alpha band activity seen in macaques [17]), while others find power reductions across both lower and higher (beta and gamma) frequency bands. Psychedelics also promote desynchronization of oscillatory rhythms in numerous established brain networks [78, 81].

While many NHP studies examining psychedelics' mechanisms of action have utilized neuroimaging methods, a few have investigated effects on specific brain regions and receptor systems more directly. The temporal lobe has been identified as a substrate for the actions of LSD in some NHP studies: bilateral temporal lobectomy was found in one study [15] to eliminate characteristic effects of LSD in chimpanzees, while another study [82] reported that LSD increased activations in medial temporal structures, including the hippocampus, of rhesus macaques. One study of mescaline, however, reported that bilateral temporal lobectomy did not affect the drug's characteristic 'oral syndrome' in rhesus macaques [18]. To the best of our knowledge, there is little data in humans demonstrating any effects of mescaline in the temporal lobe. Human studies of LSD [77, 83, 84], DMT [85, 86], and psilocybin [87–89] have found evidence for actions on the temporal lobe, though it is difficult to find a unifying connection between the various results, which range from both increases and decreases in neural activations within the temporal lobe to changes in functional connectivity (FC) between the temporal lobe and other regions [77, 83–89].

Finally, psychedelics also impact FC in NHPs. One study used functional magnetic resonance imaging (fMRI) to examine the effects of psilocybin on FC in anesthetized rhesus macaques. Certain changes to FC were induced by both psilocybin and the nonserotonergic hallucinogen salvinorin A, including increased FC between the claustrum and frontal cortex as well as DMN dissociation and decreased FC between the angular gyrus and frontal cortex. There were also changes unique to psilocybin. These changes primarily included reductions in FC (between the thalamus and angular gyrus, and between the anterior cingulate cortex and frontal cortex and caudate), but some increases in FC were also observed (between the precuneus and caudate, as well as the precuneus and claustrum and posterior parietal cortex). The changes to FC induced by both drugs were theorized to underlie the effects of hallucinogens more broadly, while those induced solely by psilocybin were interpreted as neural correlates of serotonergic psychedelic effects [90]. These results largely agree with results from human work; several studies have found that psilocybin's effects on FC include altering DMN FC and connectivity between the DMN and various brain areas, and modulating connectivity between the claustrum and cortical networks [91–93]. Similar to the desynchronization observed in human EEG studies of psychedelics, psilocybin has been observed to desynchronize brain networks and neural populations that typically coactivate in rhesus macaques, an effect that is theorized to underlie some of its FC changes [90]. These similarities between human and NHP work provide a powerful platform for conducting translational neuroscience experiments involving psychedelics' behavioral effects in NHP models.

Insights into neurobiological mechanisms from rodent studies

A number of studies in rodents have directly explored psychedelics' mechanisms of action and brain areas that may be targeted by the drugs. Many of these studies found effects in regions of the frontal cortex, in agreement with several NHP studies [17, 90]. Moreover, systemic LSD administration was shown to increase expression of c-Fos (an immediate early gene expressed following neural activation) in the rat medial prefrontal cortex (mPFC) [94], and systemic DMT administration was found to acutely and dose-dependently increase levels of serotonin and dopamine in the rat mPFC [95]. Other studies have focused on the anterior cingulate cortex (ACC), which was identified as one site of psilocybin's changes to FC in the macaque brain [90]. Systemic injections of LSD (in rats) and psilocybin (in mice) were both shown to increase c-Fos in the rodent ACC [94, 96, 97]. Psilocybin also acutely desynchronizes neural firing in the ACC of awake mice: one study measured local field potential and spiking activity after administering a single systemic dose of psilocybin and found decreases in both oscillatory power of low frequency bands (similar to human psychedelic studies) and phase modulation of most frequency bands, with overall increases in firing rates [98]. Evidence suggests that psychedelics also act on the hippocampus, an area noted to be activated in one study of LSD in rhesus macaques [82]. In mice, psilocybin was shown to increase hippocampal long-term potentiation [99]. A number of other brain areas have also been identified in rodents as possibly being activated by psychedelics, including the claustrum, raphe nucleus, nucleus accumbens, and insular cortex [96, 97]. More work is needed in animal models to continue understanding the complexities of psychedelic mechanisms of action.

FUTURE DIRECTIONS

Past NHP studies have provided a wealth of information about psychedelics' behavioral and neural effects. However, there is still much we do not understand about psychedelics and their mechanisms of action. NHPs can serve as an excellent preclinical model of psychedelic effects. Psychedelics have shown significant potential towards treating a number of psychiatric disorders, with numerous clinical trials examining the efficacy of psilocybin and LSD in reducing the symptoms of conditions like depression, anxiety, and substance use disorders [1–5]. Less research has been devoted to DMT and mescaline in this context, but preliminary evidence suggests that they may have similar therapeutic effects [45, 100, 101]. The mechanisms of action underlying these effects are complex and still largely unclear. This area of study could significantly benefit from the use of NHPs as a preclinical model of human psychedelic effects. NHPs have many similarities to humans in terms of neuroanatomy [102–104], which can be leveraged in electrophysiological studies to directly record from relevant neural populations after administration of psychedelics. Studies of psychedelics in NHPs also do not require double blinding, a feature that is notoriously difficult to achieve in clinical trials due to psychedelics' dramatic subjective effects; even with 'active' placebo control substances, individuals can often quickly deduce whether or not they have received the psychedelic [105, 106].

NHPs have an additional significant advantage over other common model species for psychedelic studies. The human 5-HT2AR has a serine at residue 242 in the binding pocket, a structure that is shared by NHP 5-HT2ARs. In rodent 5-HT2ARs, however, this position is occupied by an alanine. Mutation studies have found that replacing the serine at residue 242 with an alanine significantly increases the dissociation rate of LSD from the receptor; thus, psychedelics are likely to remain bound to the 5-HT2AR and exert effects for longer in humans and NHPs than they do in rodents, making NHPs a great preclinical model with respect to the time course of psychedelic effects [42, 107].

One recent study of the effects of DMT on depressive behaviors (induced via social isolation) in juvenile common marmosets (*Callithrix jacchus*) found that a single dose of DMT reduced certain stereotyped behaviors, increased feeding behavior and improved body weight, and returned cortisol levels to baseline in socially-isolated animals [108]. These effects persisted for 14 days after DMT administration, potentially mirroring the long-term reductions in depressive behaviors seen after single administrations of psychedelics in some human studies [2, 3, 108]. These effects in marmosets support the idea that NHPs have significant potential to serve as an excellent preclinical model of psychedelic effects. In general, however, there are several factors that need to be addressed to ensure the accuracy and efficacy of an NHP psychedelic model. Below, we have outlined several directions that we believe to be particularly relevant for future research.

Table 2. Example conversion of NHP psychedelic doses to human doses.

Drug	NHP dose and species	Example converted human dose	Dose range from human studies
Psilocybin	0.3 mg/kg, baboon [30]	0.17 mg/kg	0.03–0.42 mg/kg [2, 44, 81, 87–89, 91]
	0.4 mg/kg, stump-tailed macaque[a] [12]	0.13 mg/kg	
	2 and 4 mg/kg, rhesus macaque[a] [32]	0.65 and 1.29 mg/kg	
LSD	50 µg/kg–1 mg/kg, rhesus macaque [17, 19]	16.1 µg/kg–0.32 mg/kg	1.7–3.3 µg/kg [4, 44, 78]
DMT	1–4 mg/kg, rhesus macaque [19]	0.32–1.29 mg/kg	0.15–0.36 mg/kg [86, 101, 143, 144]
Mescaline	17 mg/kg, stump-tailed macaque [12, 14]	5.5 mg/kg	1.67–13.3 mg/kg [44, 145]
	Up to 100 mg/kg, rhesus macaque [33]	Up to 32.3 mg/kg	

[a]Dose conversions in macaques may underestimate equivalent human doses, as conversions are based on values for rhesus macaques with a weight of 3 kg [109], while average weights from rhesus and stump-tailed macaques are closer to 8 and 10 kg, respectively [146, 147].

Translating and standardizing drug doses

Doses from NHP psychedelic studies can and should be compared to human clinical doses to inform their usage, but doses should not be translated simply based on weight (mg/kg) across species, as cross-species differences can notably alter pharmacokinetics. The marmoset model of DMT's antidepressant effects [108] accounts for these differences by translating existing human doses to marmoset doses. A number of methods exist to translate between human and animal doses of a drug. Here, we employ one such method [109] to demonstrate that the doses utilized in NHP studies are not directly comparable to those in clinical studies (see Table 2). Future NHP psychedelic studies may wish to consult the literature surrounding interspecies dose scaling to select dose ranges that are analogous to common human dose ranges, ensuring a more accurate model of the effects seen at those doses. Additionally, future work in NHPs may wish to assess levels of 5-HT2AR occupancy after administering various doses of psychedelics, to determine what proportion of the drug is actually bound to the receptors at each dose, and compare these values to similar measurements from human studies [38]; matching 5-HT2AR occupancy levels across species will further allow for closer comparison of psychedelic effects in NHPs with those in humans.

NHP studies should also seek to standardize their routes of administration, which, as noted earlier, can have a substantial impact on pharmacokinetics and bioavailability; the vast majority of human psychedelic studies use oral and IV administration [1–5]. Standardizing dose ranges and routes of administration in NHP psychedelic studies to match those used in human studies may increase the effectiveness of NHPs as preclinical models of psychedelic effects. In general, there is still much to be learned about many aspects of psychedelic effects in NHPs – including standardized comparisons of the effects seen at different doses, the nuances of pharmacokinetics and pharmacodynamics, details about which behavioral effects show tolerance and the timescale of that tolerance, and more – that future research will be helpful in illuminating.

Neuroplastic effects

Increases in measures of neuroplasticity are commonly reported after systemic psychedelic administration [110–112]. In mice, psilocybin has been shown to promote plasticity in the medial frontal cortex by increasing dendritic proliferation and excitatory neurotransmission [25]. Both psilocybin [113] and DMT [114] increase neurogenesis in the mouse hippocampus, an effect that correlates with behavioral impacts like extinction of fear conditioning [113] and improved performance (compared with controls) on a memory test [114]. In studies of mice and of humans, psychedelics have been shown to increase expression of brain-derived neurotrophic factor, a key protein involved in promoting neuroplasticity [113, 115–117]. These and other mechanisms of neuroplasticity are theorized by some to underlie psychedelics' therapeutic effects [25, 99, 110, 113, 117], particularly given that increases in neuroplasticity are thought to correlate with decreases in symptoms of depression [118, 119]. However, much more work is needed to continue characterizing the connection between psychedelic-induced neuroplasticity and reductions in psychiatric symptoms. Although there are, to the best of our knowledge, not yet any studies that have examined psychedelics' neuroplastic effects in NHPs, several brain areas identified as sites of psychedelic-induced neuroplasticity in rodent studies (particularly the frontal cortex and hippocampus) were shown to be activated by psychedelics in NHPs [17, 82, 90]. Future work in NHPs examining the effects of psychedelics on measures of neuroplasticity in these areas could provide a valuable link between rodent work and clinical studies.

Drug discrimination studies

One method for studying the effects of a psychoactive compound is drug discrimination, a procedure that uses operant conditioning to train an animal to recognize the effects of a given drug. After reliable responding to a drug has been established, other drugs can be given and the animal's operant behavior monitored to see the degree of similarity in responses between the original 'training' drug and the other drugs [120–122]. A drug that induces very similar responding to the training drug is said to substitute for the original drug, and the subjective effects of the two compounds are thought to be similar [122, 123]. Thus, drug discrimination can be a powerful tool for assessing, in nonhuman species, subjective drug effects that could be described verbally in clinical studies.

While most drug discrimination studies with psychedelics have been conducted in rodents [124, 125], a few have utilized NHPs. In rats and rhesus macaques, several 5-HT2AR agonists substituted for the serotonergic psychedelic DOM and, when applied as a pretreatment, enhanced DOM's discriminative stimulus effects [126]. Combined with evidence in macaques that 5-HT2AR antagonists block DOM's discriminative stimulus effects [127, 128], these findings suggest that the subjective effects of DOM, like those of the other psychedelics reviewed here, are mediated in part by 5-HT2ARs. Other studies in macaques have found that LSD substitutes for DOM, but that the nonserotonergic hallucinogen salvinorin A (a kappa opioid receptor agonist) does not [127]. Conversely, mescaline did not produce LSD-like responding in vervet monkeys [50], despite the fact that mescaline and LSD share multiple mechanisms of action [44, 45].

Although these existing studies provide valuable information on psychedelic effects in NHPs, more work is needed to continue characterizing the receptor and neural mechanisms underlying the interoceptive effects. If, for instance, mescaline's lack of substitution for LSD [50] is replicated in future NHP drug discrimination studies, blockers of various receptors (both serotonergic and nonserotonergic) could be utilized to determine which receptors may be responsible for the disparity in effects between these drugs.

Sex differences

When considering the effects of psychedelics, particularly in a clinical context, sex differences are important to account for. Sex differences can impact factors like how a drug is absorbed, distributed, and metabolized, causing substantial variability in the effects of that drug [129–131], and many psychiatric conditions, including those that psychedelics show promise in treating, present differently based on sex [132–134]. Thus, understanding the potential effects of sex will be crucial for effective clinical application of these drugs. A recent review [135] found that there is some evidence for sex differences in responses to psychedelics, particularly in preclinical studies, but a clear pattern was difficult to discern across studies. This lack of consensus could be due to numerous factors, from differences across strains of rodents to lack of standardization across different studies. One notable contributor to our overall poor understanding of sex differences in psychedelic effects is the fact that the majority of studies (particularly human studies) include exclusively or primarily male participants [135]. Similarly, many NHP psychedelic studies were conducted in males [19, 33, 51, 53, 65, 90], though several have exclusively studied females [14, 17]. Even when both male and female NHPs were included [13, 15, 16, 20, 21, 66, 72, 127], the sex ratios were often biased towards males or unspecified. To the best of our knowledge, no study has specifically examined sex differences in the behavioral effects of psychedelics in NHPs. Future work should aim to include relatively balanced ratios of male and female NHPs, as well as to track variables that may contribute to sex differences, such as levels of sex hormones throughout estrous cycles.

Effects on social behavior

Preliminary evidence from human psychedelic studies indicates that psychedelics may increase prosocial attitudes and behaviors, ranging from feelings of closeness and caring for others to emotional empathy and altruism [136–138]. As many psychiatric disorders involve impairments to social behavior and cognition, it has been theorized, particularly in the case of psilocybin, that some of the therapeutic effects of psychedelics may be connected to these increases in prosocial behavior and empathy [139]. However, much more research is needed to understand the social effects of psychedelics and their potential connections to therapeutic outcomes. NHP studies could serve as an important component of this investigation and allow researchers to explore potential neural mechanisms underlying psychedelic-induced social effects, as NHPs display complex social repertoires and share many neural substrates of social behavior with humans [140, 141]. There are few existing studies assessing the effects of psychedelics on NHP social behavior, but several have observed decreases in rates of social grooming and increased distancing from social groups during the acute effects of psychedelics, which may appear to suggest that psychedelics have antisocial effects in NHPs. However, rates of self-grooming were also decreased at the same doses, which, in combination with effects like decreased environmental exploration, has led some authors to suggest that this decrease in social behavior may be more of a response to intense, overwhelming internally-generated stimuli induced by psychedelics, rather than an effect on social behavior per se [12, 14, 16, 19]. Additionally, prosocial effects of psychedelics can be chronic, occurring in the days and weeks following administration [137]. To the best of our knowledge, no studies have yet investigated the possibility of chronic social effects of psychedelics in NHPs.

CONCLUSIONS

NHP studies are a vital component of psychedelic research, providing invaluable insights into the behavioral effects, neural mechanisms, safety profiles, and abuse liability of these compounds in species closely related to humans. NHP models have been instrumental in identifying behavioral signatures of psychedelic drug action, including changes in both spontaneous and operant behavior, as well as pharmacological features such as tolerance. Building on this foundation, future research may expand the range of compounds studied and incorporate innovative behavioral approaches that tap into the unique advantages of the NHP model. There is also a critical opportunity to harness NHP models to investigate the mechanisms of psychedelics in psychiatric disease contexts, including depression, PTSD, and substance use disorders, where other preclinical models often fail to reflect the complexity of human cognition and emotion. We anticipate continued work in this area to yield crucial insights into the acute and long-term effects of psychedelics, therefore advancing our understanding of their neural mechanisms and therapeutic promise.

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AUTHOR CONTRIBUTIONS

JCM conceptualized the review, conducted the literature review, created figures, and wrote the manuscript. ACK contributed to the literature review, created figures, and wrote the manuscript. SWCC conceptualized the review, contributed to the literature review, and wrote the manuscript.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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