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Animal Behavior in Psychedelic Research

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***Abstract*——Psychedelic-assisted psychotherapy holds great promise in the treatment of mental health disorders. Research into 5-hydroxytryptamine 2A receptor (5-HT_{2A}R) agonist psychedelic compounds has increased dramatically over the past two decades. In humans, these compounds produce drastic effects on consciousness, and their therapeutic potential relates to changes in the processing of emotional, social, and self-referential information. The use of animal behavior to study psychedelics is under debate, and this review provides a critical perspective on the translational value of animal behavior studies**

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in psychedelic research. Acute activation of 5-HT_{2A}Rs produces head twitches and unique discriminative cues, disrupts sensorimotor gating, and stimulates motor activity while inhibiting exploration in rodents. The acute treatment with psychedelics shows discrepant results in conventional rodent tests of depression-like behaviors but generally induces anxiolytic-like effects and inhibits repetitive behavior in rodents. Psychedelics impair waiting impulsivity but show discrepant effects in other tests of cognitive function. Tests of social interaction also show conflicting results. Effects on measures of time perception depend on the experimental schedule. Lasting or delayed effects of psychedelics in rodent tests related to different behavioral domains appear to be rather sensitive to changes in experimental protocols. Studying the effects of psychedelics on animal behaviors of relevance to effects on psychiatric symptoms in humans, assessing lasting effects, publishing negative findings, and relating behaviors in rodents and humans to other more translatable readouts, such as neuroplastic changes, will improve the translational value of animal behavioral studies in psychedelic research.

***Significance Statement*——Psychedelics like LSD and psilocybin have received immense interest as potential new treatments of psychiatric disorders. Psychedelics change high-order consciousness in humans, and there is debate about the use of animal behavior studies to investigate these compounds. This review provides an overview of the behavioral effects of 5-HT_{2A}R agonist psychedelics in laboratory animals and discusses the translatability of the effects in animals to effects in humans. Possible ways to improve the utility of animal behavior in psychedelic research are discussed.**

I. Background

A new wave of psychedelic research has swept over the scientific world in the past decades, and 5-hydroxytryptamine 2A receptor (5-HT_{2A}R) agonist psychedelics are now being studied clinically for a variety of psychiatric indications (Carhart-Harris and Goodwin, 2017; Johnson and Griffiths, 2017; McClure-Begley and Roth, 2022). Before modern medicine's categorical disease classification systems, psychedelics had been used for millennia as a means to expand awareness and increase psychologic well being and sense of coherence (Hofmann, 1983; Nichols, 2016; Barrett and Griffiths, 2018; McClure-Begley and Roth, 2022). Psychedelics exert a plethora of effects on human cognition and alter emotional and sensory processing, and rodent studies mirror some of these effects (see Fig. 1). Many clinical trials with psilocybin and lysergic acid diethylamide (LSD) are currently under way for psychiatric disorders including depression, anxiety, and substance use disorders (www.clinicaltrials.gov). This development has sprouted new companies specializing in commercializing existing and developing new second-generation psychedelics for mental health treatment (McClure-Begley and Roth, 2022; Phelps et al., 2022). Psychedelic-assisted psychotherapy is a new treatment paradigm that differs fundamentally from conventional psychiatric treatments, both in the way therapists administer the treatment, the duration of the effect, and the qualitative experience by the patient. As opposed to taking the psychotherapeutic daily at home, patients who receive psychedelic-assisted psychotherapy do so typically in one or two sessions in a supportive setting with trained therapists (Nutt and Carhart-Harris, 2021; Tai et al., 2021). During the drug session, patients normally wear eyeshades and music headphones and are encouraged to submit to the experience. The specialized therapists are present during the entire session to offer support and guidance when needed, e.g., in case the patient experiences emotional distress. Patients receive preparatory drug-free sessions before the psychedelic session, and integrative therapy is applied after the drug session to help manifest the experience into therapeutically beneficial outcomes. This procedure is followed to ensure a proper set and setting, which is necessary to steer the experience in the direction of good therapeutic outcomes and to prevent harm (Hartogsohn, 2016; Brouwer and Carhart-Harris, 2021). The subjective experience of the patient is predictive of the therapeutic response. For example, patients with depression that experienced high levels of oceanic boundlessness, characterized by a feeling of unity, bliss, insightfulness, and spirituality, in response to psilocybin had higher levels of remission, whereas high levels of anxiety during the psilocybin session predicted lower levels of remission (Roseman et al., 2018). The hard teachings of research performed without proper precautions around the 1960s highlight the need for rigorous patient support in psychedelic-assisted psychotherapy to prevent iatrogenic harm (Larsen, 2021). Another distinction from conventional therapeutics is the long-lasting effect of psychedelic-assisted psychotherapy. Small-scale clinical studies in patients with

ABBREVIATIONS: 4-AcO-DMT, 4-acetoxy-N,N-dimethyltryptamine; ARRIVE, Animal Research: Reporting of In Vivo Experiments; 25B-NBOMe/CIMBI-36, 4-Bromo-2,5-dimethoxy-N-[(2-methoxyphenyl)methyl]benzeneethan-amine; 25CN-NBOH, 4-[2-[[(2-Hydroxyphenyl)methyl]amino]ethyl]-2,5-dimethoxybenzonitrile; 5-CSRTT, 5-choice serial reaction time task; DMN, default mode network; DMT, N,N-dimethyltryptamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DOM, 2,5-dimethoxy-4-methylamphetamine; DR, dopamine receptor; EPM, elevated plus maze; FST, forced swim test; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine; HTR, head twitch response; 5-HTR, 5-hydroxytryptamine receptor; 25I-NBOMe, 4-Iodoo-2,5-dimethoxy-N-[(2-methoxyphenyl)methyl]benzeneethanamine; LSD, lysergic acid diethylamide; 5-MeO-DMT, 5-methoxy-N,N-dimethyltryptamine; NB-phenethylamine, N-benzylphenethylamine; OFC, orbitofrontal cortex; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino) tetralin; PPI, prepulse inhibition; RDoC, Research Domain Criteria; TCB-2, (4-Bromo-3, 6-dimethoxybenzocyclobuten-1-yl)methylamine.

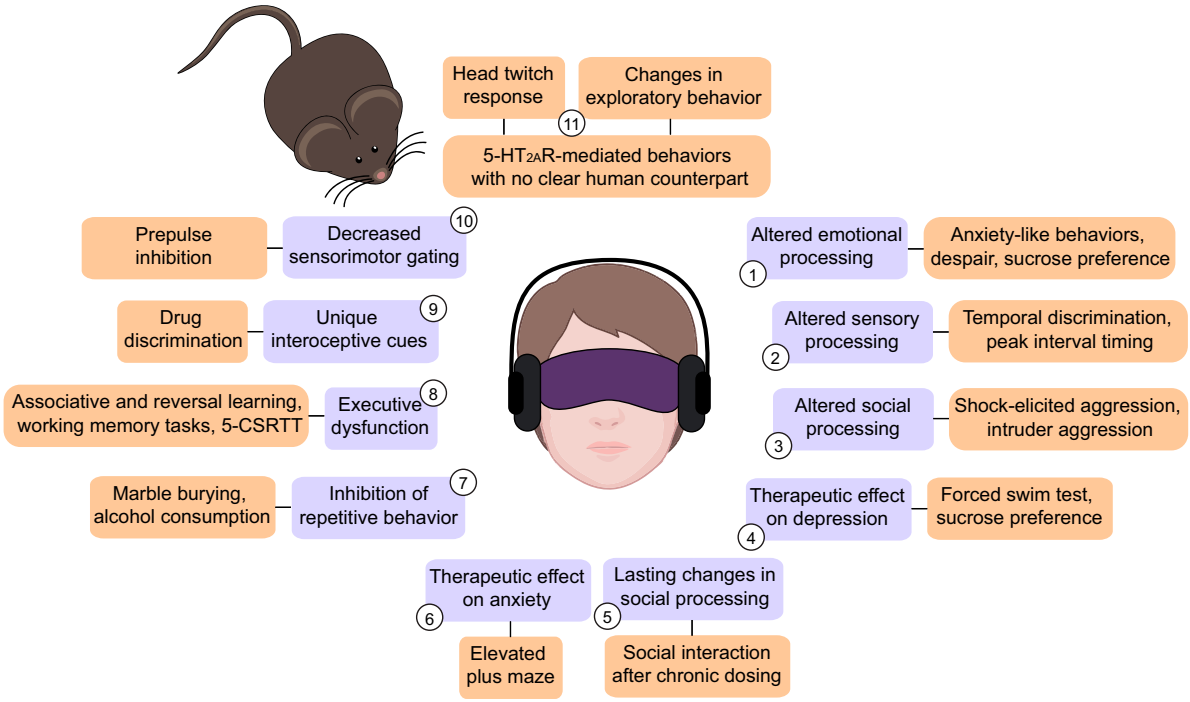

Fig. 1. Examples of effects of serotonergic psychedelics in humans and their rodent counterparts. Purple boxes represent effects in humans, whereas orange boxes represent related rodent behaviors and tests. We elaborate the effects here in a clockwise manner with exemplifying citations. (1) Humans that receive psychedelics experience changes in emotion processing, and psychedelics can induce both blissful and aversive states (Johnson et al., 2008; Vollenweider and Preller, 2020). In rodents, psychedelics alter anxiety-like behavior (Nic Dhonnchadha et al., 2003; Masse et al., 2008), despair (Cao et al., 2022), and reward processing (Parker, 1996). (2) Whereas psychedelics alter sensory processing in humans across several dimensions (Nichols, 2016), sensory distortions in rodents are reported mainly by studies measuring the perception of time (Body et al., 2006; Halberstadt et al., 2016). (3) The acute changes in social processing by psychedelics (Vollenweider and Preller, 2020) have primarily been studied in aggression-related rodent tests (Sbordone et al., 1979; Sánchez et al., 1993). (4) Although fewer studies investigate lasting therapeutic effects (Carhart-Harris et al., 2018; Goldberg et al., 2020) of psychedelics on depression-related behavior in rodents, some show that psilocybin can reduce despair in the forced swim test (Hibicke et al., 2020) and reverse stress-induced anhedonic-like responses in the sucrose preference test (Hesselgrave et al., 2021). (5) Psychedelics also produce lasting changes in prosocial behavior and values in humans (Griffiths et al., 2018), and repeated administration of LSD increases exploration of strangers in both mice and rats after the drug has been eliminated from the body (De Gregorio et al., 2021b). (6) Psychedelics produce long-lasting anxiolytic effects in humans (Goldberg et al., 2020). The anxiolytic-like effect of psilocybin in the rat elevated plus maze test appears to be context-dependent (Hibicke et al., 2020). (7) Psychedelics are suggested to reduce rigid thought and behavioral patterns in humans (Carhart-Harris et al., 2014). Accordingly, psychedelics inhibit repetitive marble burying behavior in mice (Matsushima et al., 2009; Odland et al., 2021a) and decrease compulsive consumption of alcohol in rats (Maurel et al., 1999; Meinhardt et al., 2021). (8) Acute administration of psychedelics appears to disrupt executive function in humans (Umbricht et al., 2003; Pokorny et al., 2020). Although psychedelics promote simple conditioning in rabbits (Harvey et al., 1982), other studies report deficits in reversal learning (Amodeo et al., 2020), working memory (Odland et al., 2021a), and impulsivity (Fitzpatrick et al., 2018). (9) Psychedelics produce distinct discriminative effects in both humans and rodents (Nichols, 2016), although some of the discriminative effects in rodents appear to relate to non-5-HT_{2A}R mechanisms (Winter et al., 2000; Marona-Lewicka et al., 2009). (10) Psychedelics decrease sensorimotor gating in the prepulse inhibition test in both humans and rats (Halberstadt and Geyer, 2013b), but effects in mice show discrepant results (Halberstadt and Geyer, 2018). (11) Certain rodent behavioral responses to psychedelics do not have a clear human counterpart. Examples include the head twitch response, which is used to measure 5-HT_{2A}R activation in vivo and predict psychedelic effects of new ligands (Halberstadt et al., 2020), and changes in exploratory behavior (Krebs-Thomson et al., 1998; Halberstadt et al., 2009) that particularly strengthen interpretation of results in other behavioral rodent paradigms. 5-CSRTT, 5-choice serial reaction time task.

depression, anxiety, or drug dependence indicate that psychedelic-assisted therapy may lead to remission for more than 6 months (Bogenschutz et al., 2015; Griffiths et al., 2016; Johnson et al., 2017; Carhart-Harris et al., 2018).

Qualitatively, psychedelics have been shown to enhance connection to self and others as well as acceptance of difficult emotions (Watts et al., 2017). Patients receiving conventional therapy, on the other hand, sometimes report feeling disconnected from self and others and a tendency to avoid difficult emotions (Watts et al., 2017). Despite not showing a statistically significant difference in a recent head-to-head comparison of psilocybin versus escitalopram for depression, the remission rate at the 6-week follow-up was 57% in the psilocybin group compared with 28% in the escitalopram group (Carhart-Harris et al., 2021). The remarkable therapeutic potential of psychedelics is proposed to relate to complex changes in processing of emotional, social, and self-referential information (Vollenweider and Preller, 2020), suggesting that the therapeutic effect of psychedelics may be difficult to reproduce in animals. Animal research, especially in rodents but also recently zebrafish, follows the resurgence in scientific interest. To aid drug development of 5-HT_{2A}R agonists, these compounds are examined in various animal behavioral tests to understand their effects on behaviors related to basic

pharmacology and specific psychiatric symptom domains (Hanks and González-Maeso, 2013; Neelkantan et al., 2013; Halberstadt and Geyer, 2018). Studies in humans indicate that psychedelics work by causing profound changes in the psychologic state, and especially mystical-type experiences are a strong predictor of clinical efficacy (Garcia-Romeu et al., 2014; Barrett and Griffiths, 2018; Roseman et al., 2018). It is not yet known whether these compounds can exert their therapeutic action without causing the mystical-type experience (Vollenweider and Preller, 2020; McClure-Begley and Roth, 2022), although some suggest that it may not be necessary for clinical efficacy (Olson, 2020), based on the neuroplasticity-inducing effects of psychedelics (Jones et al., 2009; Ly et al., 2018; Raval et al., 2021; Shao et al., 2021), which resemble that of ketamine (De Gregorio et al., 2021a). Psychedelics exert their distinct actions on human consciousness through activation of 5-HT_{2A}Rs (Nichols, 2016) and the 5-HT_{2A}R agonist, 25B-NBOMe (CIMBI-36), has been found to bind to cortical regions in the human brain (Ettrup et al., 2014). Psychedelics profoundly alter the information flow between cortical and subcortical brain regions by activation of 5-HT_{2A}Rs on thalamo-cortical and cortico-thalamic glutamate projections, as well as on neurons in other regions, such as the nucleus accumbens (Vollenweider and Preller, 2020). This causes increased information flow to the cortex and may underlie the subjective experience of perceptual expansion, increased awareness, and salience. Imaging studies suggest that psychedelics increase sensory processing while decreasing integrative processing, causing the net manifestation of psychedelic-induced changes in consciousness and perception (Vollenweider and Preller, 2020). Specifically, psychedelics alter activity in the default mode network (DMN), a multiarea cortical network involved in resting state processes, such as sense of self, awareness, and wakefulness (Carhart-Harris et al., 2013, 2017; Smigielski et al., 2019). The DMN is generally important for processes not related to a task and is therefore also referred to as the task-negative network; such processes include mind-wandering, autobiographical and self-referential information processing, as well as rumination and worrying (Fox et al., 2005; Lu et al., 2012). DMN disturbances are implicated in mental disorders like anxiety, depression, and attention-deficit hyperactivity disorder (Mohan et al., 2016; Doucet et al., 2020). Rodents generally have a less developed prefrontal cortex (Carlén, 2017), and although the DMN is also present in the rodent brain, it differs substantially from the human DMN (Lu et al., 2012).

Psychedelics may also work by decoupling the cortex from claustral control, thus inhibiting higher-order control networks of the brain (Nichols, 2016; Doss et al., 2022). The specificity of the psychedelic experience to higher-order consciousness in humans as well as the relatively rudimentary development of the rodent brain, when compared with the human brain, challenge the application of rodents in preclinical behavioral studies of the therapeutic effects of psychedelics. The satirical visual abstract of this review reminds us that rodents are not just small people. Several authors have questioned the utility of animal behavior in psychedelic research (Hanks and González-Maeso, 2013; Nichols, 2016; Jaster et al., 2022a), and extensive reviews of animal behavioral effects of psychedelics and their translational relevance to the effects of psychedelics in humans do not exist. As there are currently no reliable biomarkers for mental disorders (Bandelow et al., 2016, 2017; Carvalho et al., 2020), animal behavior studies remain indispensable as tools to understand the biologic underpinnings of psychiatric symptoms and to develop improved pharmacotherapeutic treatments.

This review aims to address this knowledge gap and outline the use of animal behavior in psychedelic research to date. The challenges of using rodent behavior to answer the scientific questions and perspectives on how animal behavior can best support future psychedelic drug development are discussed.

A. Pharmacology of Psychedelics

This section provides a brief overview of the different structural classes and pharmacology of psychedelics and the related translational challenges in animal behavior studies with these compounds. The factors described in this section all influence the way psychedelics affect animal behavior, and this section provides background for some of the pitfalls when interpreting results from animal studies with psychedelics. Serotonergic psychedelics act as full or partial agonists at the 5-HT_{2A}R (Nichols, 2018). Coadministration of a 5-HT_{2A}R antagonist blocks the distinct effects induced by psychedelics in humans (Vollenweider et al., 1998; Kometer et al., 2012) as well as several behavioral effects of psychedelics in rodents (Glennon et al., 1984; Halberstadt et al., 2009; Halberstadt and Geyer, 2018). Although the serotonin releasing agent 3,4-methylenedioxy methamphetamine, the N-methyl-D-aspartate receptor antagonist and dissociative anesthetic ketamine, and also cannabis are sometimes referred to as psychedelics, this review will only cover the effects of compounds that elicit their psychedelic effect by directly agonizing the 5-HT_{2A}R. Chemically, these compounds belong to three structural groups, namely tryptamines, ergolines, and phenethylamines (see Fig. 2) (Nichols, 2018). Psilocybin and LSD belong to the tryptamine and ergoline groups, respectively, and are currently the most frequently used compounds in clinical studies. 2,5-dimethoxy-4-iodoamphetamine (DOI), on the other hand, belongs to the phenethylamine structural class and is the compound that has the most extensive historical use in rodent preclinical research, but it has not been investigated in human studies (Nichols, 2016).

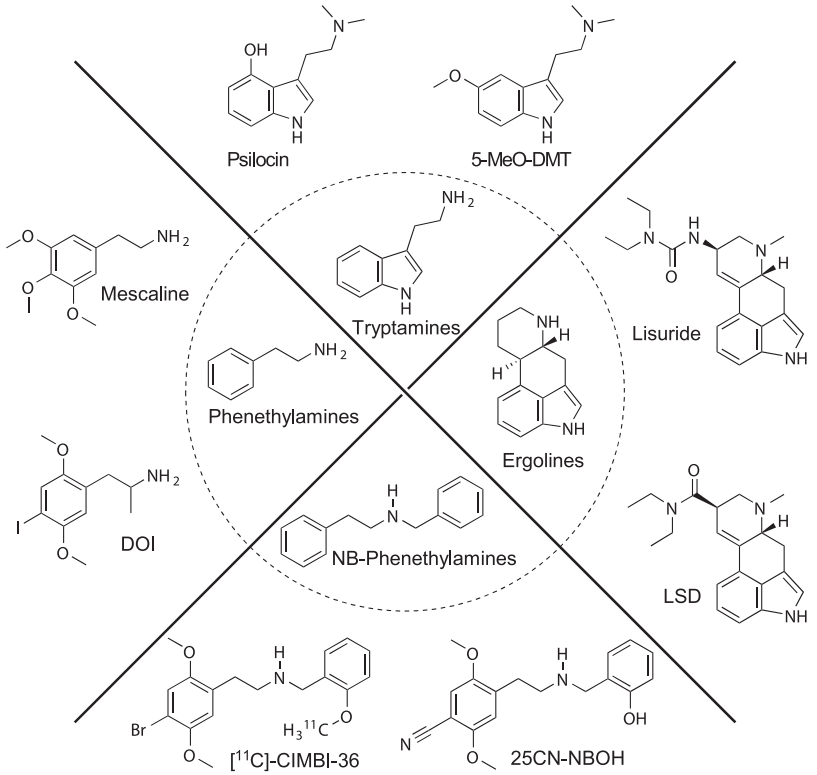

Fig. 2. Chemical structures of some tryptamines, ergolines, N-benzylphenethylamines, and phenethylamines described in this review.

This discrepancy builds on both practical and scientific reasons. As psilocybin and LSD have been classified as Schedule I drugs (drugs with no currently accepted medical use and a high potential for abuse) in the United States, and similar classifications in many other countries, DOI has been available as a research tool in many countries and can be purchased from standard commercial suppliers. DOI has been a useful preclinical research tool because it is well characterized with respect to receptor binding and activation, distribution in the body, and behavioral effects in animals (Märcher Rørsted et al., 2021). When compared with psilocybin or LSD, DOI is a more selective 5-HT_{2A}R agonist (see Fig. 3; Table 1), as DOI has ~5-fold higher binding affinity at the 5-HT_{2A}R over 5-HT_{2C}R and shows negligible binding at the 5-HT_{1A}R (Pigott et al., 2012). However, the view of DOI as a selective 5-HT_{2A}R agonist is questioned as it acts on 19 pharmacological targets within the presumed perceptible range (Ray, 2010). Building on the phenethylamine structure, Nichols and colleagues developed a series of highly potent N-benzylphenethylamine 5-HT_{2A}R agonists (see Fig. 2; Table 1) (Braden et al., 2006). Research into this structural class ultimately led to the development of [^{11}C]-CIMBI-36, a compound used as a positron emission tomography tracer for imaging studies of the human 5-HT_{2A}R (Ettrup et al., 2014), and 25CN-NBOH, a compound that shows up to 100-fold higher selectivity for 5-HT_{2A}R over 5-HT_{2C}R (Hansen et al., 2014; Jensen et al., 2017; Märcher Rørsted et al., 2021). A crude distinction is that tryptamines and ergolines are more difficult to modify into selective 5-HT_{2A}R ligands due to their native promiscuous profile. Because of their structural similarity to serotonin itself, they generally have higher affinity

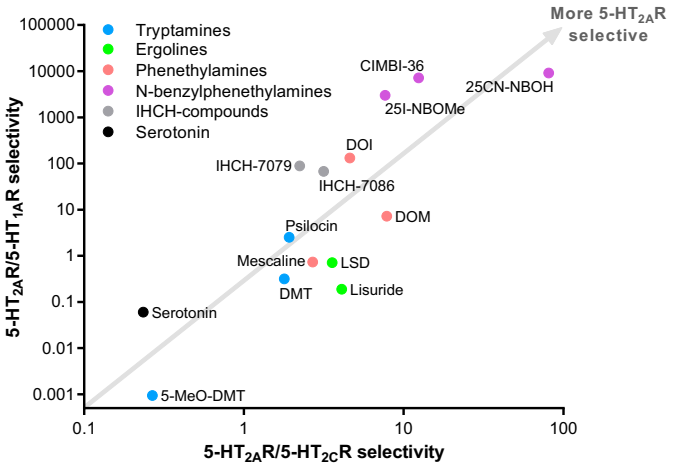

Fig. 3. Selectivity ratios of psychedelics for 5-HT_{2A}R versus 5-HT_{2C}R and 5-HT_{1A}R binding. This figure is a visual representation of the values from Table 1. High values represent a high preference for 5-HT_{2A}R binding. TCB-2 was not included in this figure due to missing affinity data at 5-HT_{2C}R and 5-HT_{1A}R. The actual selectivity ratios of DOI and 25CN-NBOH at 5-HT_{2A}R versus 5-HT_{1A}R could be higher than displayed in this figure. The gray arrow is a visual aid for the reader, not a mathematical regression of selectivity ratios. Colors of dots represent different structural families.

TABLE 1
Binding affinities and selectivity ratios of psychedelics

The table displays Ki values (nM) at 5-HT_{2A}R, 5-HT_{2C}R, and 5-HT_{1A}R. The nonpsychedelic compounds lisuride and serotonin were included as references. Selectivity ratios for 5-HT_{2A}R versus 5-HT_{2C}R and 5-HT_{1A}R were calculated based on the relative binding affinities for each compound. High numbers represent high preference for 5-HT_{2A}R binding. This table contains data from several publications, and the binding affinities cannot be directly compared between compounds. Psilocybin and 4-AcO-DMT are prodrugs of psilocin and therefore not included in the table (Nichols and Frescas, 1999). The selectivity ratios for DOI and 25CN-NBOH at 5-HT_{2A}R versus 5-HT_{1A}R were calculated based on affinities of 1000 nM and 10000 nM, respectively, and the actual selectivity ratios could be higher than stated in this table. Ki values < 3 nM are displayed with one decimal, whereas Ki values ≥ 3 nM were rounded to the nearest whole number. Selectivity ratios were calculated from the most exact numbers available.

Compound	5-HT_{2A}R Ki (nM)	5-HT_{2C}R Ki (nM)	5-HT_{1A}R Ki (nM)	Selectivity Ratio		Citations
				5-HT_{2A}R/ 5-HT_{2C}R	5-HT_{2A}R/ 5-HT_{1A}R	
Psilocin	49	94	123	1.9	2.5	(Rickli et al., 2016)
LSD	4	15	3	3.6	0.71	(Rickli et al., 2015)
DMT	237	424	75	1.8	0.32	(Rickli et al., 2016)
5-MeO-DMT	2011	538	1.9	0.27	0.00	(Ray, 2010)
DOI	8	35	>1000	4.6	>132	(Pigott et al., 2012)
Mescaline	6300	17000	4600	2.7	0.73	(Rickli et al., 2015)
DOM	507	3980	3656	7.8	7.2	(Ray, 2010)
TCB-2	0.7	ND	ND	ND	ND	(McLean et al., 2006)
25CN-NBOH	1.1	89	>10000	81	>9091	(Jensen et al., 2017)
25I-NBOMe	0.6	5	1800	7.7	3000	(Rickli et al., 2015)
25B-NBOMe (CIMBI-36)	0.5	6	3600	12	7200	(Rickli et al., 2015)
IHCH-7079	17	38	1514	2.2	89	(Cao et al., 2022)
IHCH-7086	13	40	851	3.2	68	(Cao et al., 2022)
Lisuride	1.2	5	0.2	4.1	0.19	(Cao et al., 2022)
Serotonin	25	6	1.5	0.23	0.06	(Cao et al., 2022)

ND, not determined.

to other 5-HT receptors, such as the 5-HT_{1A}R, compared with phenethylamines (see Fig. 3; Table 1) (Pigott et al., 2012; Rickli et al., 2015, 2016; Nichols, 2018). Indeed, ergolines were originally used for their 5-HT_{1A}R agonist actions, as uterotonics during childbirth and, more recently, triptan-type migraine medications (Schiff, 2006). LSD shows higher binding affinity at 5-HT_{1A}R over 5-HT_{2A}R (Rickli et al., 2015; Nichols, 2018) and has agonist activity at 12 of the 14 existing serotonergic receptors (McClure-Begley and Roth, 2022). Furthermore, LSD activates the dopamine D4 receptor (D_4R) to a degree that apparently dominates the late phase of the discriminative stimulus in the rat drug discrimination test (Marona-Lewicka et al., 2009). Psilocin, the active metabolite of psilocybin, also has a nonselective pharmacological profile, with only small preference for 5-HT_{2A}R over 5-HT_{1A}R and 5-HT_{2C}R binding (Rickli et al., 2016); ~20-fold preference in 5-HT_{2B}R over 5-HT_{2A}R binding; inhibition of serotonin reuptake; and considerable affinity at both histaminergic, dopaminergic, and adrenergic receptors (Halberstadt and Geyer, 2011). The lack of selectivity of these compounds complicates the interpretation of the pharmacological mechanism behind their behavioral effects in rodents, particularly if coadministration of a 5-HT_{2A}R antagonist or assessment of relevant biomarkers for 5-HT_{2A}R activation are not included in the study. Blocking 5-HT_{1A}Rs abolishes several psychedelic-induced behaviors in rodents (Halberstadt et al., 2011), and experiments with rats in the drug discrimination test indicate that rats are sensitive to the discriminative cues of non-5-HT_{2A}R targets of psychedelics like 5-HT_{1A}R (Winter et al., 2000; Reissig et al., 2005) and D_4R agonism (Marona-Lewicka et al., 2009). Nonpsychedelic 5-HT_{1A}R agonists can alter locomotor activity (Evenden and Angeby-Möller, 1990; Kumar et al., 2013) and produce anxiolytic-like (Moser, 1989; Collinson and Dawson, 1997; Kumar et al., 2013) and antidepressant-like effects in rodents (Kitamura et al., 2003; Miyake et al., 2014). This is not to say that rodent studies with nonselective ligands are without value, as using the same compound in humans and animals is essential to bridging the translational gap between clinical studies and neuroscience. The binding affinities of ligands described in this review at 5-HT_{2A}R, 5-HT_{2C}R, and 5-HT_{1A}R, as well as the relative selectivity ratios at 5-HT_{2A}R versus 5-HT_{2C}R and 5-HT_{1A}R are summarized in Table 1. Fig. 3 is a visual representation of the selectivity ratios.

In recent years, the development of biased 5-HT_{2A}R agonists has gained momentum (Urban et al., 2007; Nichols, 2016; Cao et al., 2022; McClure-Begley and Roth, 2022). Apart from the canonical 5-HT_{2A}R-mediated G_q signaling pathway, G_s (Liu et al., 2022) and G_i-pathways (González-Maeso et al., 2007), biased release of arachidonic acid (Kurrasch-Orbaugh et al., 2003), as well as the β-arrestin pathway (Schmid et al., 2008) can be activated by 5-HT_{2A}R agonist binding. This line of research is at an early stage, and it is not yet known which pathway(s) contribute to the clinical efficacy or subjective experience of psychedelics in humans. Interestingly, the nonselective 5-HT_{2A}R agonist lisuride does not have psychedelic effects in humans and appears to show some selectivity for the arachidonic acid pathway (Berg et al., 1998). Comparatively, rodents do not perform head twitches when administered recently developed β-arrestin-selective ligands, although such ligands retain efficacy

in mouse tests of despair-like behaviors (Cao et al., 2022). On the other hand, the G_s pathway appears crucial to 5-HT_{2A}R agonist-induced head twitch responses in mice (Liu et al., 2022). These findings indicate that rodent behavioral tests have varying sensitivities toward activation of the different intracellular pathways by 5-HT_{2A}R agonists.

Another translational limitation is linked to the differences between human and rodent 5-HT_{2A}Rs, which, although largely homologous, show some differences in their amino acid sequences (Roth, 2011). The Ser242 residue in the binding pocket of the 5-HT_{2A}R is unique to humans and is implicated in slowing the dissociation of LSD from the receptor site (McClure-Begley and Roth, 2022). The human 5-HT_{2A}R can be transfected into cell lines (González-Maeso et al., 2007; Kim et al., 2020), and ongoing studies investigate the development of mice with humanized 5-HT_{2A}Rs.

Finally, there is also a challenge extrapolating doses across species with the same compound. Dose adjustments based on body surface area can sometimes be used (Nair and Jacob, 2016) and appear sensible in cases like LSD, where body size and pharmacokinetics are correlated (Winter et al., 2005). However, this method is not feasible in cases of unconventional relationships between body size and pharmacokinetics. As an example, psilocin has an elimination half-life of approximately 150 minutes in rats (Chen et al., 2011) and approximately 180 minutes in humans (Brown et al., 2017), although some report even shorter half-lives in humans (Passie et al., 2002).

Despite these translational challenges, animal studies provide important information about 5-HT_{2A}R biology and can aid in the development of better psychiatric medicines. This review seeks to provide a nuanced presentation and interpretation of animal behavior with serotonergic psychedelics.

B. Validity of Animal Behavioral Assays

Animal models of human disease states and behavioral phenomena vary in their resemblance to the human condition. Willner defined the validity of animal models based on three domains: predictive, face, and construct validity (Willner, 1984). Predictive validity refers to the ability of a treatment intervention to produce effects in both animals and humans, face validity refers to the interspecies similarity in representation of the disease state or behavior modeled, and construct validity refers to how closely the method modeling the disease state in animals represents the disease etiology in humans. In the context of psychedelic research and modeling of psychedelic states, construct validity can refer to a necessary mechanism for the psychedelic-induced state, namely activation of 5-HT_{2A}Rs.

The head twitch response (HTR) test is an example of a test with construct validity to psychedelic effects in humans, insofar as the necessary 5-HT_{2A}R agonist component of a psychedelic experience in humans also consistently induces HTR in rodents (Halberstadt et al., 2020). In addition, the test has high predictive validity, since compounds that elicit psychedelic effects in humans reliably produce HTR in mice, with only a few false positives (Halberstadt and Geyer, 2018; Halberstadt et al., 2020). However, the HTR test lacks face validity, as psychedelics do not induce head twitches in humans.

A crude distinction in animal behavioral responses to psychedelics appears to be a tradeoff between face and predictive validity (Halberstadt and Geyer, 2010). The HTR and drug discrimination tests provide researchers with behavioral animal tests of high predictive validity to psychedelic effects in humans. Animal behaviors that have phenomenological similarity to psychedelic responses in humans are less well investigated, although several reviews have addressed this to varying degrees (Fantegrossi et al., 2008; Halberstadt and Geyer, 2010; 2018; Hanks and González-Maeso, 2013; Nichols, 2016; De Gregorio et al., 2021a).

II. Behaviors That Predict 5-HT_{2A}R Activation

A. Head Twitch Response

The HTR test quantifies head twitches, a rapid and rhythmic head movement, performed by rodents after administration of psychedelic 5-HT_{2A}R agonists (Halberstadt and Geyer, 2013a). Although false positives, such as enhancement of 5-HT signaling by fenfluramine, p-chloroamphetamine, and 5-hydroxytryptophan, do exist, the test is generally specific to 5-HT_{2A}R agonists (Halberstadt and Geyer, 2018). The test has high predictive validity for psychedelic effects in humans, and a recent study comparing 36 different 5-HT_{2A}R agonists found a convincing ($r = 0.9448$) correlation between the mouse ED_{50} and active human recreational doses (Halberstadt et al., 2020). The HTR test appears to be sensitive toward 5-HT_{2A}R agonists that induce psychedelic effects in humans, as the nonpsychedelic 5-HT_{2A}R agonist, lisuride, does not induce head twitches (Halberstadt and Geyer, 2018). After administration of a psychedelic, HTR decays faster than one would predict based on the pharmacokinetic clearance, suggesting that mice develop rapid tolerance, possibly due to 5-HT_{2A}R desensitization (Buchborn et al., 2018). Recent elucidation of the 5-HT_{2A}R structure made it possible for Cao et al. (2022) to design 5-HT_{2A}R agonists selective toward the β-arrestin signaling pathway. These agonists did not induce head twitches but retained antidepressant-like activity in mice comparable to that of LSD (Cao et al., 2022). As pathway-selective ligands have not been tested in humans, the lack of psychedelic action needs to be confirmed in clinical studies. In

contrast to the β-arrestin pathway, G_s signaling appears to be important for eliciting head twitches (Liu et al., 2022). Hence, we suggest that the HTR test might serve as an in vivo screening tool for studies of biased ligands that activate distinct intracellular signaling pathways (Urban et al., 2007; Nichols, 2016; McClure-Begley and Roth, 2022).

The original version of the HTR test was laborious due to the need of manual scoring of video material by the experimenter. More recently, the test has been automated by mounting a magnet on the skull surface of the animal (Halberstadt and Geyer, 2013a) or by using magnetic ear tags (de la Fuente Revenga et al., 2020) and using a magnetometer coil to detect movement. Recent advances in machine learning have even enabled fully automated and optimized analysis of the waveforms detected by the magnetometer coil (de la Fuente Revenga et al., 2020; Halberstadt, 2020). These developments have transformed the HTR test into a high-throughput behavioral assay for screening novel 5-HT_{2A}R agonists in vivo, for testing whether a compound reaches the brain after systemic administration, and for predicting whether the compound will elicit a psychedelic experience in humans. As mentioned in the general section on validity criteria, the face validity of the test is poor, as humans do not perform head twitches on psychedelics, and head twitch behavior does not translate to any meaningful symptom domain of human psychiatric disorders.

B. Drug Discrimination

Whereas the HTR test described above measures unconditioned behavior in rodents after 5-HT_{2A}R agonist treatment, the drug discrimination test is an operant test that assesses the interoceptive effects experienced by the animal during the influence of a drug (Winter, 2009; Halberstadt, 2015). In the standard version of the drug discrimination test, rodents are trained to respond at one lever when administered a reference compound, such as a known 5-HT_{2A}R agonist like LSD, and to another lever under the vehicle condition, although variations do exist, where two reference compounds (Appel et al., 1999) or three levers (Callahan and Appel, 1990) are used to enhance test sensitivity. During the test session, the test compound is administered, and responding to either lever is recorded. In the example of using LSD as a reference compound, responding at the LSD-associated lever indicates that the test compound is experienced more like LSD than like vehicle (Nichols, 2016). Reference and test compounds with different pharmacology than 5-HT_{2A}R agonists, or coadministration of selective antagonists during the test can be used to dissect the specific cues of multimodal agents (Halberstadt, 2015).

The drug discrimination test has better face validity than the HTR test but is laborious due to the required training. This test generally has high predictive validity to psychedelics in humans, and there is a correlation between the rat ED_{50} and human recreational doses (Nichols, 2016). Nevertheless, LSD (Reissig et al., 2005), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) (Winter et al., 2000), but not psilocybin (Winter et al., 2007), have been found to exert 5-HT_{1A}R-associated discriminative cues, and lisuride, a nonpsychedelic 5-HT_{2A}R agonist, produces false positive responding in this test as it can substitute for LSD (Appel et al., 1999). Furthermore, the late phase of the discriminative stimulus of LSD appears to depend on D_4R agonism (Marona-Lewicka et al., 2009).

This section described the two commonly used predictive behavioral tests to study serotonergic psychedelics. Psychedelics also elicit other behaviors of lesser utility in psychedelic drug development. One example is the mouse ear scratch response that is sensitive to the R-enantiomers of phenethylamine-type 5-HT_{2A}R agonists, but not tryptamines, possibly because of their activation of 5-HT_{1B}Rs, which blocks the ear scratch response to 5-HT_{2A}R agonism. This compromises the predictive validity of the ear scratch test (Halberstadt and Geyer, 2010). Several reviews have given comprehensive overviews of the effects of 5-HT_{2A}R agonists in drug discrimination and HTR tests (Fantegrossi et al., 2008; Nichols, 2016; Halberstadt and Geyer, 2018). The remaining part of this review will focus on animal behavioral tests of possible phenomenological relevance to human responses to psychedelics.

III. Animal Behaviors with Possible Phenomenological Relatedness to Psychedelic Effects in Humans

A. Acute Effects

This section covers the acute effects of 5-HT_{2A}R agonists on animal behavior while the compound is still present in the bloodstream and includes actions of acute, chronic, and repeated subchronic dosing of psychedelics. Behavioral effects that go beyond the presence of the compound in the bloodstream are described in the section *Lasting effects*. Table 2 displays a cited overview of the acute effects of psychedelics described in this chapter.

1. Prepulse Inhibition. The prepulse inhibition (PPI) test can be used to assess the effects of a compound on sensorimotor gating, which is a measure of preattentive information filtering (Swerdlow et al., 2008). In the PPI test, subjects are exposed to a brief loud auditory stimulus that triggers a startle response. When a low-intensity stimulus is presented immediately before the pulse, an autonomous sensory filtering mechanism is engaged, which attenuates the startle response to the subsequent pulse (Swerdlow

TABLE 2
Overview of acute behavioral effects of psychedelics
This table is not an exhaustive overview of all existing literature. For well investigated behavioral domains comprehensively reviewed by others, we cite examples of original studies along with recommended reviews. Head twitch response and drug discrimination behaviors were described in the section "*Behaviors That Predict 5-HT$_{2A}$R Activation*" and are not included in this table. Exposure refers to whether effects were recorded after a single dose or after repeated doses. Citations are listed in chronological order. Drug, exposure, and species are listed in alphabetical order.

Domain	Behavior	Result	Interpretation	Citations	Drug	Exposure	Species
Sensorimotor gating	Prepulse inhibition of acoustic startle response	↓	Impaired sensorimotor gating	(Sipes and Geyer, 1995; Ouagazzal et al., 2001; Krebs-Thomson et al., 2006; Pálenícek et al., 2008; Allen et al., 2011; Wischhof et al., 2012; Hazama et al., 2014) see also reviews (Halberstadt and Geyer, 2013b, 2018; Nichols, 2016)	DOI, LSD, mescaline, 5-MeO-DMT	Single	Mouse, rat
		↔	No effect	(Dulawa and Geyer, 2000)	DOM	Single	Mouse
		↑	Enhanced sensorimotor gating	(Freedland and Mansbach, 1999) see also review by Halberstadt and Geyer (2011)	DMT	Single	Mouse
Exploratory motility/ locomotor activity	Distance traveled	↑	Increased locomotor activity	(Halberstadt et al., 2009; Buchborn et al., 2018; Odland et al., 2021a; De Gregorio et al., 2022) see also reviews (Nichols, 2016; Halberstadt and Geyer, 2018)	DOI, LSD, 25CN-NBOH	Single	Mouse
		↓	Decreased locomotor activity	(Halberstadt et al., 2011)	Psilocin, 5-MeO-DMT	Single	Mouse
	Behavioral pattern monitor investigation	↓	Reduced exploration or disorganized behavior	(Krebs-Thomson et al., 1998, 2006) see also reviews (Nichols, 2016; Halberstadt and Geyer, 2018)	DOI, LSD, 5-MeO-DMT	Single	Rat
Anxiety-related behavior	Four-plate test exploration	↑	Decreased anxiety	(Nic Dhonnchadha et al., 2003; Masse et al., 2008)	DOI	Single	Mouse
		↓	Increased anxiety	(Masse et al., 2008)	DOI	Single	Mouse
	Elevated plus maze test exploration	↑	Decreased anxiety	(Nic Dhonnchadha et al., 2003)	DOI	Single	Mouse
		↔	No effect	(De Gregorio et al., 2022)	LSD	Single	Mouse
	Light/dark test exploration	↔	No effect	(Nic Dhonnchadha et al., 2003; De Gregorio et al., 2022)	DOI, LSD	Single	Mouse
	Novelty-suppressed feeding	↔	No effect	(De Gregorio et al., 2022)	LSD	Single	Mouse
	Fear extinction	↑	Decreased anxiety	(Zhang et al., 2013)	TCB-2	Single	Mouse
	Expression of conditioned fear	↓	Decreased anxiety	(Hughes et al., 2012; Hagsäter et al., 2021)	DOI, psilocybin, TCB-2, 25CN-NBOH	Single	Rat
Anxiety-related behavior	Open field center exploration	↔	No effect	(De Gregorio et al., 2022)	LSD	Single	Mouse
		↓	Increased anxiety	(Adams and Geyer, 1985; Krebs-Thomson et al., 2006; Halberstadt et al., 2011)	LSD, psilocin, 5-MeO-DMT	Single	Mouse, rat
	Surface swimming	↑	Decreased anxiety	(Grossman et al., 2010; Kyzar et al., 2012)	LSD, mescaline	Single	Zebrafish
Despair-like behavior	Forced swim immobility	↓	Antidepressant-like	(Cao et al., 2022)	IHCH-7079, IHCH-7086, LSD	Single	Mouse
		↔	No effect	(Wang et al., 2008; Jefsen et al., 2019; De Gregorio et al., 2022)	DOI, LSD, psilocybin	Single	Mouse, rat

(*continued*)

TABLE 2—*Continued*

Domain	Behavior	Result	Interpretation	Citations	Drug	Exposure	Species
		↑	Depressogenic-like	(Cui et al., 2018)	DOI	Single	Mouse
	Tail suspension immobility	↓	Antidepressant-like	(Cao et al., 2022)	IHCH-7079, IHCH-7086, LSD	Single	Mouse
Pleasure	Conditioned place preference	↑	Increased pleasure/reward association	(Parker, 1996; Meehan and Schechter, 1998; Jeon et al., 2019)	LSD, 25I-NBOMe	Repeated	Mouse, rat
	Sucrose/ saccharin preference	↑	Prohedonic	(Maurel et al., 2000)	DOI	Single	Rat
		↓	Anhedonic-like	(Parker, 1996)	LSD	Repeated	Rat
Compulsivity	Marble burying	↓	Anticompulsive-like	(Matsushima et al., 2009; Egashira et al., 2012; Jensen et al., 2020; Odland et al., 2021a, 2021b)	DOI, psilocybin, 25CN-NBOH	Single	Mouse
	Stereotypic behaviors in the open field	↑	Compulsive-like	(De Gregorio et al., 2022)	LSD	Single	Mouse
	Spontaneous alternation	↑	Anticompulsive-like	(Odland et al., 2021a)	DOI, 25CN-NBOH	Single	Mouse
		↓	Compulsive-like	(Yadin et al., 1991)	5-MeO-DMT	Single	Rat
	Schedule-induced polydipsia	↓	Anticompulsive-like	(Navarro et al., 2015; Mora et al., 2018)	DOI	Single	Rat
Dependence/ addiction	Alcohol consumption or seeking	↓	Antiaddictive	(Maurel et al., 1999, 2000; Oppong-Damoah et al., 2019; Berquist and Fantegrossi, 2021; Meinhardt et al., 2021; Elsilä et al., 2022)	DOI, LSD, psilocybin	Single	Mouse, rat
	Intracranial self-stimulation	↓	Not addictive but causes behavioral disruption	(Katsidoni et al., 2011; Sakloth et al., 2019; Jaster et al., 2022)	DOI, LSD, mescaline, psilocybin, TCB-2	Repeated, single	Rat
		↔	No effect	(Elsilä et al., 2022)	LSD	Single	Mouse
	Nictitating membrane response	↑	Increased associative learning	(Gimpl et al., 1979; Harvey et al., 1982; Siegel and Freedman, 1988)	DOM, LSD	Repeated	Rabbit
	Spatial learning	↓	Impaired spatial learning and memory	(Rambousek et al., 2014)	Psilocin	Repeated	Rat
	Memory reacquisition	↓	Impaired spatial memory	(Rambousek et al., 2014)	Psilocin	Single	Rat
	Memory consolidation	↑	Improved memory consolidation	(Meneses and Hong, 1997; Zhang et al., 2013)	DOI, TCB-2	Single	Mouse, rat
		↔	No effect	(Rambousek et al., 2014)	Psilocin	Single	Rat
		↓	Impaired memory consolidation	(Meneses, 2007)	DOI	Single	Rat
Learning and memory	Working memory	↔	No effect	(Ruotsalainen et al., 1998; Odland et al., 2021a)	DOI, 25CN-NBOH	Single	Mouse, rat
		↓	Impaired working memory	(Ko and Evenden, 2009; Odland et al., 2021a)	DOI	Single	Mouse, rat
Cognitive flexibility	Reversal learning	↑	Improved flexibility	(King et al., 1974)	LSD	Single	Rat
		↔	No effect	(Amodeo et al., 2020; Odland et al., 2021c)	DOI, 25CN-NBOH	Repeated, single	Mouse
		↓	Impaired flexibility	(Amodeo et al., 2020)	25CN-NBOH	Single	Mouse
Impulsivity	Waiting impulsivity	↑	Increased waiting impulsivity	(Koskinen et al., 2000a, 2000b; Wischhof and Koch, 2012; Fitzpatrick et al., 2018)	DOI	Single	Mouse, rat
		↔	No effect	(Fletcher et al., 2007)	DOI	Single	Rat

(*continued*)

TABLE 2—*Continued*

Domain	Behavior	Result	Interpretation	Citations	Drug	Exposure	Species
	Impulsive choice	↔	No effect	(Elsilä et al., 2020)	LSD, 25CN-NBOH	Single	Mouse
Social interaction	Shock-elicited aggression	↑	Increased aggression	(Sbordone et al., 1979)	Mescaline	Single	Rat
		↔	No effect	(Sbordone et al., 1979)	LSD	Single	Rat
		↓	Decreased aggression	(Walters et al., 1978; Sbordone et al., 1979)	DMT, psilocin, 5-MeO-DMT	Single	Rat
	Isolation aggression	↑	Increased aggression	(Sakaue et al., 2002)	DOI	Single	Mouse
		↔	No effect	(Krsiak, 1979)	LSD	Single	Mouse
		↓	Decreased aggression	(Sánchez et al., 1993)	DOI, 5-MeO-DMT	Single	Mouse
	Resident intruder aggression	↓	Decreased aggression	(Olivier and Mos, 1992)	DOI	Single	Rat
	Maternal aggression	↓	Decreased aggression	(Olivier and Mos, 1992)	DOI	Single	Rat
	Social defeat conditioning	↑	More submissive	(Clinard et al., 2015)	TCB-2	Single	Hamster
	Direct social interaction	↔	No effect	(De Gregorio et al., 2021b)	LSD	Single	Mouse
Time perception	Peak interval timing switch time	↓	Overestimation of time	(Body et al., 2003, 2006)	DOI	Single	Rat
	Temporal discrimination switch time	↑	Underestimation of time	(Asgari et al., 2006; Hampson et al., 2010; Halberstadt et al., 2016)	DOI, 25CN-NBOH	Single	Mouse, rat
Visual processing	Light intensity perception	↔	No effect	(Hampson et al., 2010)	DOI	Single	Rat

et al., 2008). The PPI test has high face validity as it is highly similar in both animals and humans (Swerdlow et al., 2008; Halberstadt and Geyer, 2013b). PPI is impaired in schizophrenia and other psychiatric and neurologic disorders (Braff et al., 1978; Bolino et al., 1994; Kohl et al., 2013). Deficits in PPI reflect an inability of brainstem gating circuitries to prevent excessive information from reaching forebrain networks (Swerdlow and Geyer, 1998; Swerdlow et al., 2001).

A wide variety of pharmacological modulators can enhance or disrupt PPI (Swerdlow et al., 2008). PPI is disrupted by psychotomimetic drugs, such as the N-methyl-D-aspartate receptor antagonist phencyclidine or high doses of amphetamine, effects that are generally reversed by antipsychotic medication (Braff et al., 2001; Geyer et al., 2001; Swerdlow et al., 2008). PPI has therefore been used extensively as a test to predict antipsychotic drug effects or to study certain aspects of psychosis.

5-HT_{2A}R antagonism is a characteristic of many antipsychotic drugs and likely contributes to the improvement in PPI observed with these drugs (Sipes and Geyer, 1994; Geyer et al., 2001). Accordingly, 5-HT_{2A}R agonists can impair PPI in both humans (Vollenweider et al., 2007) and rodents (Allen et al., 2011; Ouagazzal et al., 2001), and PPI has often been used as a readout when investigating psychedelics as "psychosis-inducing models" in rodents (Halberstadt and Geyer, 2013b; Nichols, 2016). However, the effects of psychedelics in this test might also contribute to our understanding of how these compounds facilitate therapeutic effects on psychiatric symptoms. Changes in the filtering of internal and external sensory and emotional information might have relevance to the psychotherapeutic effect (Carhart-Harris, 2018), and the test remains a valuable and highly translatable mechanistic tool for studying psychedelics in animals. Converging reports show that various 5-HT_{2A}R agonists disrupt PPI in rats (Sipes and Geyer, 1995; Ouagazzal et al., 2001; Krebs-Thomson et al., 2006; Pálenícek et al., 2008; Wischhof et al., 2012; Halberstadt and Geyer, 2013b, 2018; Nichols, 2016), suggesting that they impair sensorimotor gating, whereas studies on 5-HT_{2A}R agonists in mice show less consistent results (Freedland and Mansbach, 1999; Dulawa and Geyer, 2000; Allen et al., 2011; Halberstadt and Geyer, 2011, 2018; Hazama et al., 2014), compromising the predictive sensitivity of the test to psychedelics. Studying the nature of psychedelic-induced impairments in PPI may help elucidate the phenomenon of expanded perception of external and internal sensory information that characterizes psychedelic experiences.

2. Locomotor Activity. Changes in locomotor activity of animals in response to psychedelics do not have any obvious translational therapeutic applications in human psychopharmacology. Although psychedelics increase certain measures of consciousness, they do not necessarily increase arousal (Scott and Carhart-Harris, 2019). Neural complexity in the brain has been reliably quantified with the so-called perturbational-complexity index, which quantifies the complexity of electroencephalogram responses to pulses of transcranial magnetic stimulation (Casali et al., 2013). It describes the level of neural activity related to consciousness, and is high during normal wakefulness and low when consciousness is low, e.g., during sleep, anesthesia, or some forms of brain injury (Casali et al., 2013; Scott and Carhart-Harris, 2019). Imaging studies reveal that psychedelics increase neural complexity above levels of normal wakefulness in humans, and they are discussed as potential new treatments for disorders of consciousness, e.g., vegetative or minimally conscious states. The effect on complexity proposedly relates more to increased richness of the conscious experience, rather than nonspecific changes in arousal (Scott and Carhart-Harris, 2019). However, psilocybin in humans slightly increases head motion of subjects in a functional magnetic resonance imaging scanner (Roseman et al., 2014) and increases the area of handwriting in subjects set with the task of copying a text (Fischer et al., 1969).

Changes in motor activity in rodents are not specific to psychedelics, and the test is therefore not useful for the screening of new psychedelic compounds. Testing 5-HT_{2A}R agonists in animal locomotor tests can provide some insights into how 5-HT_{2A}Rs modulate basic exploratory behavior and be a supplementary measure when evaluating results from other behavioral tests where the readout is based on motor responses. The 5-HT_2R-selective agonist DOI produces a bell-shaped effect on nonspecific locomotor activity, with lower doses showing a 5-HT_{2A}R-dependent locomotor-stimulant effect and higher doses showing a 5-HT_{2C}R-dependent locomotor suppression (Halberstadt et al., 2009). Accordingly, the more selective 5-HT_{2A}R agonist 25CN-NBOH increases locomotor activity in mice (Buchborn et al., 2018; Odland et al., 2021a). Psilocin and 5-MeO-DMT, on the other hand, decrease locomotor activity in mice through a 5-HT_{1A}R-dependent mechanism (Halberstadt et al., 2011). In contrast, acute administration of LSD, which also activates 5-HT_{1A}Rs, does not affect locomotor activity in mice in lower doses but increases locomotion at a high dose, presumably due to the dopaminergic effects of LSD (De Gregorio et al., 2022).

Looking into broader classifications of motor activity than merely distance traveled, Mark Geyer's laboratory developed the behavioral pattern monitor that also measures investigatory nose pokes and rearings and assesses the smoothness and predictability of movement into the assessment of behavior. DOI

produces an overall 5-HT_{2A}R-dependent decrease in exploration in the behavioral pattern monitor and causes the locomotor activity pattern to become less organized, although the disruptive effect of LSD on locomotor pattern in this test appears to also involve 5-HT_{2C}Rs (Krebs-Thomson et al., 1998). The tryptamine psychedelic 5-MeO-DMT produces a 5-HT_{1A}R-dependent decrease in exploratory behavior in the behavioral pattern monitor (Krebs-Thomson et al., 2006).

In summary, phenethylamine psychedelics stimulate gross motor activity, whereas tryptamines inhibit it, and psychedelics generally cause the motor activity to become less organized.

3. Anxiety-Like Behaviors. Psychedelics show promising preliminary effects in the treatment of anxiety in humans (Gasser et al., 2015; Griffiths et al., 2016; Goldberg et al., 2020). Despite these long-term beneficial effects, the acute psychedelic state may trigger chaotic experiences, sometimes described as "bad trips", that can be characterized by intense anxiety, panic, and dysphoria (Johnson et al., 2008). The risk of this is low in modern clinical studies, and such experiences mostly occur if the psychedelic agent is used without proper set and setting. Animal tests of anxiety include both unconditioned, conflict-based tests, such as elevated plus maze (EPM) and light/dark box, and conditioned tests, such as the four-plate and fear conditioning/extinction tests (Campos et al., 2013). Most of these tests were developed around the 1980s for screening anxiolytic drug candidates, and their validity as anxiety tests relies heavily on their predictive validity of classic anxiolytic compounds, such as benzodiazepines and selective serotonin reuptake inhibitors (Campos et al., 2013).

Microinjection of DOI into the hippocampus has an anxiolytic-like effect in the mouse four-plate test but an anxiogenic-like effect when injected into the amygdala or periaqueductal gray (Masse et al., 2008). When administered systemically, DOI has anxiolytic-like effects in the mouse four-plate test and EPM test but does not affect exploration in the light/dark test (Nic Dhonnchadha et al., 2003). In support of the anxiolytic-like effect, TCB-2, another phenethylamine, has been shown to facilitate rapid fear extinction in mice (Zhang et al., 2013). DOI reduces fear-potentiated startle response in rats, an effect that is blocked by coadministration of the 5-HT_{2A}R antagonist ketanserin but not by the 5-$HT_{2B/2C}$R antagonist SB206553 (Hughes et al., 2012). Accordingly, 5-HT_{2A}R-dependent mechanisms for expression of conditioned fear in rats were recently reported for 25CN-NBOH and psilocybin but not for TCB-2 (Hagsäter et al., 2021). In addition to these effects in rodents, anxiolytic-like effects of psychedelics have been observed in zebrafish, where LSD (Grossman et al., 2010) and mescaline (Kyzar et al., 2012) promote swimming close to the water surface, indicating reduced anxiety.

In contrast, psilocin has shown an anxiogenic-like effect in mice, as reflected by reduced time spent in the center in the behavioral pattern monitor, but this effect was found to be related to 5-HT_{1A}R activation (Halberstadt et al., 2011). Decreases in central area exploration of an open area have also been reported with LSD (Adams and Geyer, 1985) and 5-MeO-DMT (Krebs-Thomson et al., 2006) in rats. Similar to the mouse study with psilocin, Krebs-Thomson and colleagues found that the effect of 5-MeO-DMT on center area exploration was 5-HT_{1A}R-dependent (Krebs-Thomson et al., 2006). Finally, a recent study found no acute effects of LSD in the mouse EPM, light/dark test, novelty-suppressed feeding, or central area exploration in the open field (De Gregorio et al., 2022).

In summary, acute administration of psychedelics to rodents and zebrafish primarily appears to have anxiolytic-like properties, except for the anxiogenic-like decreases in center exploration of the open field test that appear to relate to a non-5-HT_{2A}R mechanism.

4. Depression-Related Behaviors. Treatment of depression is a major area of interest in modern psychedelic research (Carhart-Harris et al., 2018, 2021; Goldberg et al., 2020). The acute psychedelic experience alters emotion processing in humans (Vollenweider and Preller, 2020) and can affect mood in different ways (Johnson et al., 2008). Conventional rodent tests of antidepressant efficacy include the forced swim test (FST), which measures the ability of a drug to reduce despair-like responses to inescapable stress, and the sucrose preference test, in which preference for a sweetened solution purportedly measures the hedonic tone. Although changes in hedonic tone and despair have some face validity to human symptoms of depression (Fried et al., 2016), the specific behaviors assessed in rodents radically differ from those in humans. The predictive validity of such tests is based on their sensitivities toward conventional monoamine-based antidepressants (Gururajan et al., 2019). This creates a catch-22 situation: conventional animal tests of antidepressant action risk overlooking compounds with other pharmacological actions, and as long as well established clinical evidence for antidepressant effects of treatments with alternative mechanisms is lacking, such animal tests cannot be validated for their sensitivities toward novel mechanisms.

Cao and colleagues recently investigated the effects of LSD and the two new β-arrestin-biased 5-HT_{2A}R agonists IHCH-7079 and IHCH-7086 on despair-like behavior in mice (Cao et al., 2022). The authors exposed the mice to either restraint stress or chronic administration of corticosterone before behavioral testing in the FST and tail suspension test. LSD, IHCH-7079, and IHCH-7086 ameliorated stress-induced despair in

both tests in a 5-HT_{2A}R-dependent manner. Interestingly, the new β-arrestin-biased compounds did not induce head twitches, and as compounds that induce mouse head twitches normally produce psychedelic effects in humans (Halberstadt et al., 2020), the authors suggest that the compounds could potentially serve as nonhallucinogenic 5-HT_{2A}R agonist antidepressants. These results are intriguing, but it should be noted that nonpsychedelic 5-HT_{2A}R agonists have not been evaluated in clinical trials for long-term efficacy in depression. A few studies on chronic lisuride treatment investigate effects on depressive symptoms (Gillin et al., 1994; Hougaku et al., 1994), but interpretation of these studies are challenged by the nonselective pharmacology of lisuride. In the study by Cao et al. (2022), lisuride showed similar null effects in the HTR test but appeared to be less effective than IHCH-7079 and IHCH-7086 in the FST and tail suspension test. Contrary to these antidepressant-like effects, DOI has been shown to prevent the antidepressant like effect of 9 hours of fasting in the mouse FST (Cui et al., 2018). Other studies found no effect of DOI (Wang et al., 2008) or LSD (De Gregorio et al., 2022) on immobility in the mouse FST. This lack of effect could be related to the use of healthy, nonstressed mice, compared with Cao et al. (2022) that used restraint stress or corticosterone treatment of the animals to induce a deficit that was reversed by 5-HT_{2A}R agonists. A study on the late acute effects (4 hours post injection) of psilocybin in the Flinders Sensitive Line rat model of depression similarly did not find any effect on FST behavior (Jefsen et al., 2019).

Anhedonia is a core symptom of depression (Fried et al., 2016), but rodent studies on the effects of 5-HT_{2A}R agonists on reward processing and pleasure are still few. LSD has been shown to decrease conditioned sucrose taste preference while promoting conditioned place preference in rats (Parker, 1996). The increase in conditioned place preference by LSD has been confirmed in male but not female rats (Meehan and Schechter, 1998). More recently, Jeon et al. (2019) investigated the reinforcing properties of the novel 5-HT_{2A}R agonist 25I-NBOMe. They found that 25I-NBOMe promoted conditioned place preference in mice, suggesting that animals preferred the 25I-NBOMe condition to vehicle. In another set of experiments in the study, 25I-NBOMe did not increase self-administration in rats (Jeon et al., 2019). These results suggest that psychedelics may increase the hedonic tone without causing dependence liability. A study that investigated alcohol consumption and included the option of sweetened palatable fluids in the study design found that DOI increased saccharin but not sucrose consumption in rats (Maurel et al., 2000).

In summary, tests of despair-like behavior and behaviors related to hedonic responses in rodents have shown inconsistent acute effects of 5-HT_{2A}R agonists.

5. Compulsive-Like Behaviors and Drug Dependence. Psychedelics have been suggested to promote a more flexible mindset in patients by destabilizing the default patterns of brain signaling that cause stereotyped behavior and thoughts (Carhart-Harris et al., 2014; Carhart-Harris and Nutt, 2017; Carhart-Harris and Friston, 2019). A small pilot study of psilocybin in patients with obsessive-compulsive disorder showed promising results, even at low doses (Moreno et al., 2006), and psilocybin also appears to be effective in treating substance use disorders (Garcia-Romeu et al., 2014; Johnson et al., 2014, 2017; Bogenschutz et al., 2015). Rodent tests of compulsive-like behaviors measure different types of repetitive behaviors in rodents. Although the tendency to perform repetitive behaviors has some similarity across species, the type of behavior is often vastly different between rodents and humans, compromising the face validity of these tests. The predictive validity of tests of compulsive-like behavior relies on their sensitivity toward conventional anticompulsive serotonergic drugs, such as selective serotonin reuptake inhibitors (Albelda and Joel, 2012; Alonso et al., 2015).

The marble burying test has often been used to study anxiolytic drugs (Njung'e and Handley, 1991; Nicolas et al., 2006), but repetitive digging more likely reflects perseverative behavior not related to anxiety (Thomas et al., 2009; Dixit et al., 2020). Psilocybin, 25CN-NBOH, and DOI all robustly reduce marble burying in mice (Matsushima et al., 2009; Egashira et al., 2012; Jensen et al., 2020; Odland et al., 2021a, 2021b). A 5-HT_{2A}R antagonist blocked the effect of DOI, but not psilocybin, indicating that psilocybin reduces digging behavior through a 5-HT_{2A}R-independent mechanism (Odland et al., 2021b). DOI and 25CN-NBOH also partly attenuated compulsive-like behavior induced by the 5-HT_{1A}R agonist 8-OH-DPAT in the mouse spontaneous alternation behavior test (Odland et al., 2021a). Conversely, the tryptamine psychedelic 5-MeO-DMT impairs spontaneous alternation behavior in the original rat version of this test (Yadin et al., 1991), although this effect possibly relates to its 5-HT_{1A}R agonist actions, as 5-MeO-DMT reduces exploratory behavior in the behavioral pattern monitor in a 5-HT_{1A}R-dependent manner (Krebs-Thomson et al., 2006). In one study, a high dose of LSD increased stereotypic-like grooming and rearing in mice, but this effect was suggested to relate to the dopaminergic effects of high LSD doses (De Gregorio et al., 2022).

Rat studies show that both local administration in the medial prefrontal cortex (Mora et al., 2018) and systemic administration (Navarro et al., 2015) of DOI cause 5-HT_{2A}R-dependent attenuation of schedule-induced polydipsia, a type of compulsive-like drinking of water performed by rats under intermittent food reinforcement schedules. In line with these effects, DOI reduced alcohol intake in alcohol-preferring rats in a

5-HT_{2A}R-dependent manner, an effect that was stable in the presence of other palatable fluids (Maurel et al., 1999, 2000). A recent study confirmed the reducing effect of DOI on alcohol intake in rats and found that the effect was largest in animals with a high baseline intake of alcohol (Berquist and Fantegrossi, 2021). LSD and DOI have similarly been shown to acutely reduce alcohol consumption in mice (Oppong-Damoah et al., 2019; Elsilä et al., 2022), and the effect of DOI appears to depend on 5-HT_{2A}R activation and is selective to animals with a high baseline consumption of alcohol (Oppong-Damoah et al., 2019). Accordingly, psilocybin also decreases alcohol-seeking lever-press behavior in alcohol-dependent rats and concurrently restores the alcohol dependence-induced downregulation of metabotropic glutamate receptor subtype 2, an important marker of alcohol-induced neuroadaptations that is also involved in cognitive flexibility (Meinhardt et al., 2021). In investigations of the potential dependence-inducing properties of 5-HT_{2A}R agonists, Jaster et al. (2022b) found that DOI, LSD, mescaline, and psilocybin all decreased intracranial self-stimulation in rats, and similar results were previously reported with LSD, mescaline, and psilocybin by Sakloth et al. (2019). As dependence-inducing compounds normally increase intracranial self-stimulation, these findings suggest that psychedelics cause behavioral disruptio, but are not intrinsically addictive (Jaster et al., 2022). Accordingly, TCB-2 increases the threshold for intracranial self-stimulation in rats, which is opposite of the effect of cocaine (Katsidoni et al., 2011). In contrast, LSD does not appear to alter intracranial self-stimulation in mice, possibly suggesting a species difference in sensitivity to the effect of psychedelics on this behavior (Elsilä et al., 2022). When coadministered with amphetamine (Elsilä et al., 2022), cocaine (Katsidoni et al., 2011), or methamphetamine (Sakloth et al., 2019), psychedelics do not alter the effects of the psychostimulants on intracranial self-stimulation.

In summary, acute administration of 5-HT_{2A}R agonists to rodents primarily inhibits different types of repetitive and drug dependence-related behaviors.

6. Cognition. Various types of cognitive deficits present as part of the pathology across different psychiatric disorders (Millan et al., 2012). Psychedelics can profoundly change thought patterns. By relaxing high-level beliefs and thereby alter the processing of new information, psychedelic-assisted psychotherapy can potentially serve as a valuable transdiagnostic treatment in psychiatry (Carhart-Harris and Friston, 2019). Furthermore, psychedelics may disengage the claustral control of cortical areas and thereby impair attentional control (Doss et al., 2022). The acute effects of psychedelics in human tests of executive function include psilocybin-induced deficits in attention in the AX-type continuous performance test (Umbricht et al., 2003) and in working memory (Wittmann et al., 2007), as well as LSD-induced impairment of cognitive flexibility (Pokorny et al., 2020). Some rodent cognition tests have higher face validity to the human tests, compared with the tests related to other behavioral domains described in previous paragraphs. The development of automated systems, such as touchscreens or lever-press operant platforms, enables assessment of behavior without disturbing the animals. These systems also allow the rodent task to be analogous to human versions (Kim et al., 2015; Izquierdo et al., 2017; Hailwood et al., 2018). Nevertheless, this chapter also includes results obtained using classic conditioning and simpler maze-based tests.

Studies with LSD and 2,5-dimethoxy-4-methylamphetamine (DOM) suggest that 5-HT_{2A}R agonists promote low-level associative learning in rabbits by facilitating classic conditioning of the nictitating membrane response (Gimpl et al., 1979; Harvey et al., 1982; Siegel and Freedman, 1988). In a more recent study in rats, Rambousek et al. (2014) tested psilocin, the active metabolite of psilocybin, in several maze-based cognitive tasks in rats. Rats explored the carousel maze, in which an entry into one sector resulted in administration of electric shocks. Psilocin administration impaired spatial learning and memory, as psilocin-treated rats failed to avoid the punished area, and this deficit persisted during a drug-free session performed at the end of the experiment. An alternative explanation of this deficit is that psilocin may have changed the salience of the punishment and thereby affected learning. In a second experiment, the authors trained rats in the Morris water maze without the influence of psilocin. After the drug-free training period, rats that were administered psilocin prior to the test session failed to retrieve the memory of the platform location, and this deficit persisted into another drug-free test session. Finally, the authors also looked into memory consolidation in the Morris water maze, where psilocin was administered immediately after a drug-free training session. Performance in a drug-free test session on the following day was unaltered between treatment groups, suggesting that psilocin did not affect memory consolidation (Rambousek et al., 2014). Other studies of memory consolidation by DOI in a rat autoshaping task report both improvement with low doses (Meneses and Hong, 1997) and impairment by a higher dose (Meneses, 2007). Another study showed that TCB-2 facilitated consolidation of both fear memory and novel object recognition in mice (Zhang et al., 2013). The deficit in spatial memory reported by Rambousek and colleagues is mirrored by a recent study, where mice were treated with 5-HT_{2A}R agonists before the test and allowed to explore a Y-maze freely without any reinforcement or punishment (Odland et al., 2021a). Mice treated with DOI had lower alternation rates, suggestive of a deficit in spatial working memory or impaired behavioral

flexibility, whereas 25CN-NBOH did not affect alternation rate. Both compounds reversed a deficit in performance induced by the 5-HT_{1A}R agonist 8-OH-DPAT, as described above in the section about compulsive-like behavior (Odland et al., 2021a). Accordingly, DOI also decreased the accuracy of correct responses in the rat version of the n-back task, similar to a test commonly used to study working memory in humans. The impairment was seen only at doses that also impaired general responding, which might confound the results (Ko and Evenden, 2009). Another study reported similar nonspecific effects with DOI in rats performing an operant conditioned working memory task (Ruotsalainen et al., 1998), but DOI did not affect accuracy in the latter study, leaving the question of how 5-HT_{2A}R agonists affect working memory in rodents in need of further exploration.

Cognitive flexibility is a cognitive domain often assessed with the rodent reversal learning task (Izquierdo et al., 2017). In an older study, LSD facilitated correct responding in the rat reversal learning task by increasing the probability of a correct response at the end of reversal training from ~50% in vehicle-treated rats to ~75% in rats treated with LSD (King et al., 1974). By contrast, a recent study in mice in a probabilistic spatial reversal learning test showed that 25CN-NBOH impaired reversal learning, whereas DOI did not (Amodeo et al., 2020). The authors hypothesized that activation of 5-HT_{2A}R and 5-HT_{2C}R exerted opposing effects on cognitive flexibility that could have produced the null effect of the less selective 5-HT_2R agonist DOI. When combining DOI with coadministration of a 5-HT_{2C}R antagonist, the authors found that DOI also impaired reversal learning, suggesting that selective 5-HT_{2A}R agonism can impair cognitive flexibility. Another recent study using the mouse touchscreen-based reversal learning task, which is more similar to the human task (Izquierdo et al., 2017), did not show any significant effects of repeated doses of 25CN-NBOH on cognitive flexibility during reversal learning (Odland et al., 2021c).

The 5-choice serial reaction time task is an operant conditioned rodent test for assessing attention and impulsivity. DOI reliably increases impulsive-like behavior in this test by increasing premature responses to a blank screen before stimulus presentation in rats (Koskinen et al., 2000a, 2000b; Wischhof and Koch, 2012) and mice (Fitzpatrick et al., 2018). One study did not find any effect of DOI on premature responses in rats, which might have been confounded by a general nonspecific decrease in chamber activity (Fletcher et al., 2007). Although premature responses represent impulsive actions due to a deficit in waiting impulsivity, the rodent Iowa gambling task assesses the nuances of impulsive-like decision-making when choosing between high-risk and low-risk options. A recent study in mice showed that neither LSD nor 25CN-NBOH affected option selection in this task (Elsilä et al., 2020).

In summary, cognitive effects of psychedelics vary according to the type of cognitive domain that is tested. Apart from a consistent increase in waiting impulsivity in the 5-choice serial reaction time task, effects of 5-HT_{2A}R agonists on other measures of executive function in rodents show incongruent results, highlighting the need of further research in this field. A deeper understanding of how psychedelics affect different cognitive domains in both rodents and humans could lead to identification of translatable models, possibly by refining or elaborating existing models of psychedelic drug action in humans, such as relaxed beliefs under psychedelics (Carhart-Harris and Friston, 2019) or the claustral control hypotheses (Doss et al., 2022). It is possible that deficits in some cognitive domains contribute to the therapeutic action of psychedelics. Delineating the potential link between cognitive and therapeutic effects of psychedelics might prove useful when establishing a rodent platform to better understand their therapeutic effect.

7. Social Interaction. Deficits in social cognition are common in psychiatric disorders and may impede prognosis of the patient (Patin and Hurlemann, 2015), and some consider psychiatric illnesses as disorders of social interaction (Schilbach, 2016). Human studies with LSD show that there is no simple explanation for how psychedelics acutely affect social abilities. In one study, subjects performed questionnaire-type psychology tests of behaviors relevant to social cognition. Participants receiving LSD scored higher on empathy, had increased prosocial responses in an economic resource allocation task, and were impaired in their ability to recognize sad and fearful faces (Dolder et al., 2016). Another study used a social interaction test in which participants interacted with a virtual character. Simultaneous eye tracking assessed interaction with the character, and functional magnetic resonance imaging measured neural effects of LSD. In contrast to the previous study, LSD reduced neural activity in areas relevant to social cognition and impaired the establishment of joint attention, an important measure of social interaction (Preller et al., 2018).

In rodents, the studies investigating acute effects of psychedelics have mainly assessed aggressive behaviors. Hence, the focus of the rodent studies lies on negative social encounters, rather than on subtle behaviors or perceptions related to empathy, which are the focus of most human studies. One study tested different 5-HT_{2A}R agonists in male rats in a shock-elicited aggression situation test. Rats treated with mescaline were more aggressive to their opponent when compared with controls, whereas high doses of N,N-dimethyltryptamine (DMT) or psilocin

decreased aggression, and no effects were observed with LSD (Sbordone et al., 1979). Another study similarly found that high doses of DMT or 5-MeO-DMT reduced shock-elicited aggressive behavior in rats (Walters et al., 1978). It should be noted that 5-HT_{1A}R agonists are known to reduce aggressive behaviors (Olivier and Mos, 1992; Sánchez et al., 1993), suggesting that prosocial effects of tryptamine-type psychedelics may also involve 5-HT_{1A}R agonism. In line with the LSD result reported by Sbordone and colleagues, a study in socially isolated mice also showed no significant effects of LSD on aggressive behavior (Krsiak, 1979). In line with the mescaline results, the phenethylamine DOI increased the time spent fighting in isolation-housed mice when exposed to an intruder (Sakaue et al., 2002). Interestingly, the DOI-induced aggression could be blocked by coadministration of a 5-HT_{1A}R agonist, supporting the theory that 5-HT_{2A}R and 5-HT_{1A}R affect aggression in rodents in opposite directions (Sakaue et al., 2002). In contrast, Sánchez and colleagues showed that high doses of DOI decreased intruder aggression in isolated male mice, mimicking the effect of low doses of 5-MeO-DMT (Sánchez et al., 1993). Similar antiaggressive effects of DOI have been observed in rats in both the resident intruder and maternal aggression tests (Olivier and Mos, 1992). The results from these latter two studies appear to conflict with the hypothesis that 5-HT_{2A}R agonism causes proaggressive effects; however, the effects of high dose DOI could also likely result from 5-HT_{2C}R agonism, which may reduce aggressive behavior (Rosenzweig-Lipson et al., 2007).

More recently, Clinard and colleagues tested the effects of injections of TCB-2 in the basolateral amygdala on social defeat conditioning in Syrian hamsters (Clinard et al., 2015). The animals received the injections before social defeat training, consisting of exposure to an aggressive opponent. Conditioned defeat testing on the subsequent drug-free day consisted of exposure to a nonaggressive intruder. Animals that received TCB-2 during defeat training were more submissive to the nonaggressive intruder on the following day, but they did not differ from saline-treated controls in other types of social behavior or aggression (Clinard et al., 2015). Another recent study employing the direct social interaction test found no effect of acute LSD administration on social interaction between mice (De Gregorio et al., 2021b).

Overall, rodent studies on aggressive behavior have shown mixed results. Although this may not generalize to other types of social behavior, it is noteworthy that human psychology studies of social behavior have also shown mixed results.

8. Sensory Perception. Psychedelics alter the way humans perceive time (Wittmann et al., 2007; Yanakieva et al., 2019), suggesting that 5-HT_{2A}Rs are involved in cognitive domains of temporal processing. Changes in time perception in rodents are not exclusive to 5-HT_{2A}R agonists (Mobini et al., 2000; Cevik, 2003; Hampson et al., 2010). The high face validity of the rodent tasks makes them valuable tools to study the regulatory role of the 5-HT_{2A}R more specifically by using selective pharmacological compounds at different doses. Tasks that assess time perception in rodents include the peak interval timing task and the temporal discrimination task (Hanks and González-Maeso, 2013). Here, animals trained in operant conditioning tasks respond to levers to obtain food rewards based on time-related stimuli. The peak interval timing task requires the animal to respond to different levers at different time points within the session; hence, it focuses on the perception of the current time period. The temporal discrimination task, on the other hand, requires the animal to respond to different levers according to the duration of a stimulus that has already passed (Hanks and González-Maeso, 2013). Studies in rats show that DOI produces a 5-HT_{2A}R-dependent decrease in switching time in peak interval timing tasks, indicating that DOI causes rats to overestimate the duration of a current time period (Body et al., 2003; 2006). Conversely, the same group found that DOI causes rats to underestimate the duration of a time period that has already passed in the temporal discrimination task (Asgari et al., 2006; Hampson et al., 2010). More recently, a study in the mouse temporal discrimination task reported similar effects with 25CN-NBOH and DOI and found that 5-HT_{2A}R and 5-HT_{2C}Rs alter perception of time in opposing directions (Halberstadt et al., 2016). The discrepant findings between task types possibly relate to a 5-HT_{2A}R-mediated disruption of sustained attention during long time intervals in the temporal discrimination task (Hampson et al., 2010; Halberstadt et al., 2016).

In contrast to the well known effect of psychedelics on visual processing in humans (Nichols, 2016; Vollenweider and Preller, 2020), the Hampson study found no effect of DOI on discrimination of light intensity in rats (Hampson et al., 2010). The effects of psychedelics on information processing in other sensory modalities in rodents are less investigated, but chronic treatment with DOM has been shown to selectively decrease 5-HT_2R expression in the olfactory nucleus of rats (Doat-Meyerhoefer et al., 2005), suggesting a possible involvement of 5-HT_{2A}Rs on the perception of smell.

B. Lasting Effects

Clinical efficacy of psychedelic-assisted psychotherapy in humans lasts well into follow-ups performed several months after the administration of the 5-HT_{2A}R agonist (Johnson et al., 2014; Bogenschutz et al., 2015; Gasser et al., 2015; Carhart-Harris et al., 2018). In healthy volunteers, changes in the openness personality domain are still present after 1 year (MacLean et al., 2011), and participants also report lasting changes in prosocial attitudes (Griffiths et al., 2018). Identifying behavioral effects that persist past the pharmacokinetic profile

of the compound in laboratory animals is a central element to the translational value of animal experiments with psychedelics. In comparison with the numerous studies on acute behavioral effects of 5-HT_{2A}R agonists, reports of lasting effects in rodents are more limited. When investigating delayed or lasting behavioral effects of psychedelics in rodents, a critical question is: which time points in the rodent are best suited to mirror the follow-up time of several months or even a year used in clinical studies? This section covers behavioral effects observed in rodents beyond the presence of the compound in the bloodstream.

Several biologic effects of 5-HT_{2A}R agonists can be detected beyond the acute effects. Receptor desensitization (Porter et al., 2001; Buchborn et al., 2018), changes in gene expression (Martin and Nichols, 2018; de la Fuente Revenga et al., 2021), and neuronal growth (Jones et al., 2009; Ly et al., 2018; Raval et al., 2021; Shao et al., 2021) likely influence the reported behaviors at different time points. Most rodent studies in this chapter assessed the behavioral effects 1 day after administration of the psychedelic compound, which is very short compared with the monthly follow-ups in human studies, even after accounting for the short life span of rodents. One study assessed effects of DMT after only 1 hour, due to the short half-life of DMT in the rat (Cameron et al., 2018). A few studies assessed behavioral effects 1 month after drug administration (King and Ellison, 1989; Marona-Lewicka et al., 2011; Alper et al., 2018; Hibicke et al., 2020). Table 3 displays a cited overview of the lasting effects of psychedelics described in this chapter.

1. Prepulse Inhibition. Disruption of sensorimotor gating by psychedelics appears to be limited to acute administration, as neither single (de la Fuente Revenga et al., 2021) nor repeated (Tsybko et al., 2020) dosing of 5-HT_{2A}R agonists have lasting effects on PPI when assessed 1 day after administration in mice. However, repeated doses of 25CN-NBOH increased startle amplitude in mice 1 day after the last dose (Tsybko et al., 2020).

2. Locomotor Activity. One study found that repeated (every other day for more than 3 months) administration of LSD to rats caused hyperactivity that persisted for at least 4 weeks after the last dose (Marona-Lewicka et al., 2011). In contrast, a single dose of DMT has been shown to reduce motor activity in rats 1 hour after administration (Cameron et al., 2018), and similar effects are reported with repeated intra-orbitofrontal cortex (OFC) injections of DOI 2 days after the last injection (Xu et al., 2016). Other studies with single or repeated administration of different psychedelics to rats and mice report no lasting effects on motor activity (Cameron et al., 2019; Tsybko et al., 2020; De Gregorio et al., 2021b, 2022; de la Fuente Revenga et al., 2021). These few studies and their different experimental designs are not sufficient to make conclusions about long-lasting effects of psychedelics on locomotor activity.

3. Anxiety-Like Behaviors. A recent study found that a single dose of psilocybin had an anxiolytic-like effect in the EPM test 6 weeks after administration in rats exposed to weekly exploration of a novel environment but not in rats exposed to a novel environment only once (Hibicke et al., 2020). The necessity of repeated exposure to the novel environment for the lasting anxiolytic effect of psilocybin indicates that effects on anxiety-like behavior are context-dependent. This is relevant for the translational value of the study design, since effects of psychedelics in humans are largely dependent on the setting in which the drug is taken (Hartogsohn, 2016; Brouwer and Carhart-Harris, 2021).

A study on mice exposed to repeated restraint stress and receiving seven daily doses of LSD showed an anxiolytic-like response to LSD in stressed animals in the light/dark and novelty-suppressed feeding tests and increased the number of central area entries in the open field test when tested 1 day after the last dose (De Gregorio et al., 2022). LSD did not affect anxiety-like behavior in the EPM test in stressed or nonstressed animals. This study also showed that repeated, but not acute, administration of LSD increased the firing of serotonergic neurons and blunted the inhibitory effect of the 5-HT_{1A}R agonist 8-OH-DPAT on firing frequency, suggestive of a desensitization of 5-HT_{1A} autoreceptors as an adaptive response to repeated LSD administration (De Gregorio et al., 2022). An alternative interpretation is that 5-HT_{1A}Rs modulate the efficacy of psychedelics on rodent measures of anxiety, such that actions at 5-HT_{1A}Rs may confound the interpretation of animal experiments with tryptamine and ergoline psychedelics. Repeated LSD also increased spine density in medial prefrontal cortex pyramidal neurons in both stressed and nonstressed animals, an effect that may be involved in the anxiolytic-like effect (De Gregorio et al., 2022).

In another study, a single dose of DMT caused anxiogenic-like effects in rats in the EPM test 1 hour after administration (Cameron et al., 2018). Interestingly, DMT also promoted fear extinction learning, and this effect persisted when rats were tested on the following day. The same research group found similar anxiolytic-like effects of repeated low doses of DMT on fear extinction in rats but no effects on anxiety in the rat open field or EPM tests (Cameron et al., 2019). In accordance with these effects of DMT, DOI reduced fear generalization in a novel setting and promoted fear extinction 24–48 hours after administration in mice (de la Fuente Revenga et al., 2021), and similar effects are also reported with psilocybin in mice treated with a single dose of psilocybin and exposed

TABLE 3
Overview of lasting behavioral effects of psychedelics
This table is not an exhaustive overview of all existing literature. Exposure refers to whether effects were recorded after a single dose or after repeated doses. Parentheses represent time delay between drug administration and behavioral recording and includes the range of time delays cumulatively investigated for the given behavior in the listed studies. Citations are listed in chronological order. Drug, exposure, and species are listed in alphabetical order.

Domain	Behavior (Time Delay)	Result	Interpretation	Citations	Drug	Exposure	Species
Sensorimotor gating	Prepulse inhibition of acoustic startle response (24 h)	↔	No effect	(Tsybko et al., 2020; de la Fuente Revenga et al., 2021)	DOI, TCB-2, 25CN-NBOH	Repeated, single	Mouse
Locomotor activity	Distance traveled (1 h–28 days)	↑	Increased locomotor activity	(Marona-Lewicka et al., 2011)	LSD	Repeated	Rat
		↔	No effect	(Cameron et al., 2019; Tsybko et al., 2020; De Gregorio et al., 2021b, 2022; de la Fuente Revenga et al., 2021)	DMT, DOI, LSD, TCB-2, 25CN-NBOH	Repeated, single	Mouse, rat
		↓	Decreased locomotor activity	(Xu et al., 2016; Cameron et al., 2018)	DMT, DOI	Repeated, single	Rat
Anxiety-related behavior	Elevated plus maze test exploration (1 h–41 days)	↑	Decreased anxiety	(Hibicke et al., 2020)	Psilocybin	Single	Rat
		↔	No effect	(Cameron et al., 2019; De Gregorio et al., 2022)	DMT, LSD	Repeated	Mouse, rat
		↓	Increased anxiety	(Cameron et al., 2018; Horsley et al., 2018)	DMT, psilocin	Repeated, single	Rat
	Light/dark test exploration (24 h)	↑	Decreased anxiety	(De Gregorio et al., 2022)	LSD	Repeated	Mouse
		↔	No effect	(Tsybko et al., 2020; de la Fuente Revenga et al., 2021)	DOI, TCB-2, 25CN-NBOH	Repeated, single	Mouse
	Fear extinction (1 h–3 days)	↑	Decreased anxiety	(Catlow et al., 2013; Cameron et al., 2018, 2019; de la Fuente Revenga et al., 2021)	DMT, DOI, psilocybin	Repeated, single	Mouse, rat
	Open field center exploration (24–48 h)	↑	Decreased anxiety	(De Gregorio et al., 2022)	LSD	Repeated	Mouse
		↔	No effect	(Cameron et al., 2019; Tsybko et al., 2020; De Gregorio et al., 2021b)	DMT, DOI, LSD, TCB-2	Repeated	Mouse, rat
		↓	Increased anxiety	(Clinard et al., 2015; Xu et al., 2016; Tsybko et al., 2020)	DOI, TCB-2, 25CN-NBOH	Repeated, single	Hamster, mouse, rat
	Novelty-suppressed feeding (24 h)	↑	Decreased anxiety	(De Gregorio et al., 2022)	LSD	Repeated	Mouse
		↔	No effect	(De Gregorio et al., 2021b)	LSD	Repeated	Mouse
Despair-like behavior	Forced swim immobility (1 h–35 days)	↓	Antidepressant-like	(Cameron et al., 2018, 2019; Hibicke et al., 2020; de la Fuente Revenga et al., 2021)	DMT, DOI, LSD, psilocybin	Repeated, single	Mouse, rat
		↔	No effect	(Jefsen et al., 2019; De Gregorio et al., 2021b, 2022; Hesselgrave et al., 2021)	LSD, psilocin, psilocybin	Repeated, single	Mouse, rat
	Tail suspension immobility (3 days)	↑	Depressogenic-like	(Xu et al., 2016)	DOI	Repeated	Rat
	Learned helplessness (24 h)	↓	Antidepressant-like	(Shao et al., 2021)	Psilocybin	Single	Mouse
	Avoidance learning in bulbectomised rats (22 h)	↑	Antidepressant-like	(Buchborn et al., 2014)	LSD	Repeated	Rat
Pleasure	Sucrose/saccharin preference (22–48 h)	↑	Prohedonic	(Hesselgrave et al., 2021)	Psilocybin	Single	Mouse
		↔	No effect	(De Gregorio et al., 2021b, 2022; Kimmey et al., 2022)	LSD, TCB-2	Repeated, single	Mouse
		↓	Anhedonic-like	(Marona-Lewicka et al., 2011; Xu et al., 2016)	DOI, LSD	Repeated	Rat
	Female urine preference (24–48 h)	↑	Prohedonic	(Hesselgrave et al., 2021)	Psilocybin	Single	Mouse
Compulsivity	Stereotypic behaviors in the open field (1–24 h)	↔	No effect	(Cameron et al., 2018; De Gregorio et al., 2021b, 2022)	DMT, LSD	Repeated, single	Mouse, rat
	Marble burying (24 h)	↔	No effect	(Tsybko et al., 2020)	DOI, TCB-2, 25CN-NBOH	Repeated	Mouse

(*continued*)

TABLE 3—*Continued*

Domain	Behavior (Time Delay)	Result	Interpretation	Citations	Drug	Exposure	Species
Dependence/ addiction	Alcohol intake (22 h–46 days)	↔	No effect	(Meinhardt et al., 2020; Elsilä et al., 2022)	LSD, psilocybin	Repeated, single	Mouse, rat
		↓	Antiaddictive	(Alper et al., 2018; Kimmey et al., 2022)	LSD, TCB-2	Repeated, single	Mouse
	Opiate withdrawal (24 h)	↓	Antiaddictive	(Vargas-Pérez et al., 2017)	4-AcO-DMT	Single	Rat
	Nicotine withdrawal (24 h)	↓	Antiaddictive	(Vargas-Pérez et al., 2017)	4-AcO-DMT	Repeated, single	Mouse
	Nicotine conditioning (24 h)	↓	Antiaddictive	(Vargas-Pérez et al., 2017)	4-AcO-DMT	Single	Mouse
	Nondependent-like response to morphine (24 h)	↑	Antiaddictive	(Vargas-Pérez et al., 2017)	4-AcO-DMT	Single	Mouse, rat
Learning and memory	Novel object recognition (24 h–10 days)	↑	Improved memory	(Morales-Garcia et al., 2020)	DMT	Repeated	Mouse
		↔	No effect	(Cameron et al., 2019; de la Fuente Revenga et al., 2021)	DMT, DOI	Repeated, single	Mouse, rat
	Spatial learning (24 h–10 days)	↑	Improved learning	(Morales-Garcia et al., 2020)	DMT	Repeated	Mouse
		↔	No effect	(Tsybko et al., 2020)	DOI, TCB-2, 25CN-NBOH	Repeated	Mouse
	Working memory (24 h)	↔	No effect	(Cameron et al., 2019)	DMT	Repeated	Rat
Social interaction	Aggression (24 h–30 days)	↑	Increased aggression	(Marona-Lewicka et al., 2011; Clinard et al., 2015)	LSD, TCB-2	Repeated, single	Hamster, rat
	Explorative sniffing (48 h–30 days)	↑	Increased exploration	(Marona-Lewicka et al., 2011; Clinard et al., 2015)	LSD, TCB-2	Repeated, single	Hamster, rat
	Direct social interaction (24 h–37 days)	↑	Increased social interaction	(King and Ellison, 1989; De Gregorio et al., 2021b)	LSD	Repeated	Mouse, rat
		↔	No effect	(De Gregorio et al., 2021b)	LSD	Single	Mouse
		↓	Decreased social interaction	(Marona-Lewicka et al., 2011)	LSD	Repeated	Rat
	Three chamber interaction (24–48 h)	↑	Increased social interaction	(De Gregorio et al., 2021b)	LSD	Repeated	Mouse
		↔	No effect	(Cameron et al., 2019)	DMT	Repeated	Rat

to fear extinction training 3 days later (Catlow et al., 2013). In contrast, a study using three "micro-doses" of psilocin over 6 days in rats (~10% of the dose used by Hibicke and colleagues) found that psilocin can produce mild anxiogenic-like effects in the EPM test 48 hours after the last psilocin administration (Horsley et al., 2018). Supporting the anxiogenic-like effect, another study tested the effects of microinjections of TCB-2 into the basolateral amygdala in Syrian hamsters (Clinard et al., 2015). After receiving TCB-2, animals were exposed to either social defeat training or to an empty aggressor cage. All animals were tested in the open field test 48 hours later. TCB-2 reduced the time spent in the center of an open field by both groups of animals (Clinard et al., 2015). Similar anxiogenic-like decreases in central area exploration in the open field test are reported in rats tested 48 hours after the last intra-OFC injection of DOI (Xu et al., 2016) and after repeated systemic administration of 25CN-NBOH, but not DOI or TCB-2, in mice (Tsybko et al., 2020). LSD showed no lasting effects on central area exploration in the open field or on latency to feed in the novelty-suppressed feeding test in healthy mice (De Gregorio et al., 2021b). Similarly, there was no lasting effect on anxiety-like behavior in the light/dark test after a single administration of DOI (de la Fuente Revenga et al., 2021) or repeated administrations of DOI, 25CN-NBOH, or TCB-2 (Tsybko et al., 2020).

In summary, several studies on delayed or lasting effects of psychedelics have reported enhanced fear extinction in mice and rats. Studies on lasting effects on other types of anxiety-related behaviors have shown conflicting results.

4. Depression-Related Behaviors. Rats treated with a single dose of psilocybin or LSD display reduced despair-like behavior, as reflected by increased swimming and decreased immobility in the FST when tested 5 weeks after drug administration (Hibicke et al., 2020). Three high doses of DMT have been shown to increase swimming and reduce immobility in the rat FST 1 hour after administration of the last dose, a time point at which DMT had been cleared from the bloodstream (Cameron et al., 2018), and repeated administration of low-dose DMT produces a similar effect (Cameron et al., 2019). However, it is unclear whether this effect was 5-HT_{2A}R-dependent, as there were no significant changes in molecular markers relevant to 5-HT_{2A}R activation (Cameron et al., 2019), as reported by others (Martin and Nichols, 2018). DOI also reduces immobility in the mouse FST when tested 24 hours or 7 days after administration, mirroring the lasting effects observed in rats (de la Fuente Revenga et al., 2021). Although significant effects were observed at both time points, the effect size at 7 days after injection was only a ~10% reduction in immobility compared with ~40% at 24 hours, indicating that the lasting effect decays (de la Fuente Revenga et al., 2021). In contrast, other studies report no effect of psychedelics on despair-like behavior in the FST in rats or mice (Jefsen et al., 2019; De Gregorio et al., 2021b, 2022; Hesselgrave et al., 2021). One study even found that repeated intra-OFC administration of DOI increased despair-like behavior in the rat tail suspension test 3 days after the last injection (Xu et al., 2016).

In support of lasting effects of psychedelics on despair-like behavior in rodents, Shao et al. (2021) recently tested the effect of psilocybin in the learned helplessness test in mice and found that psilocybin reduced escape failure when tested 1 day after treatment. Psilocybin also increased the number of dendritic spines 1 month after administration, but the authors did not assess behavior at that time point (Shao et al., 2021). Finally, Buchborn et al. (2014) tested repeated administration of LSD on depression-like deficits in active avoidance learning in bulbectomised rats and performed behavioral testing approximately 22 hours after drug administration. Removal of olfactory bulbs induces a variety of behavioral disturbances in rodents that are sensitive to treatment with conventional antidepressant agents (Kelly et al., 1997; Song and Leonard, 2005). LSD showed an antidepressant-like effect by reversing escape failure induced by olfactory bulbectomy but did not affect avoidance behavior in sham-operated animals (Buchborn et al., 2014).

Various studies have examined potentially lasting effects on measures of hedonic-like responses. In male mice, psilocybin restored stress-induced deficits in the preference for both sucrose and female urine when tested 24–48 hours after psilocybin treatment (Hesselgrave et al., 2021), suggesting that psychedelics can have prolonged antidepressant-like effects on measures of reward sensitivity. As mentioned above, this study did not find any change in immobility in the FST at 1, 3, or 7 days after psilocybin administration. Remarkably, both the antianhedonic and the neuroplasticity-inducing effects of psilocybin observed in this study were independent of 5-HT_{2A}R activation (Hesselgrave et al., 2021). In contrast, repeated intra-OFC injections of DOI (Xu et al., 2016) and repeated systemic administration of LSD (Marona-Lewicka et al., 2011) decreased sucrose preference in rats when tested 24–34 hours after the last drug administration. Other studies report no lasting changes in saccharin consumption by mice treated with TCB-2 (Kimmey et al., 2022) or sucrose preference by both stressed and nonstressed mice that received repeated LSD injections (De Gregorio et al., 2021b, 2022). These reports indicate that the lasting effects of psychedelics on rodent behaviors related to despair and reward processing vary according to differences in protocol.

5. Compulsive-Like Behaviors and Drug Dependence. Repeated administration of LSD in mice (De Gregorio et al., 2021b, 2022) or a single dose of DMT in rats (Cameron et al., 2018) produced no lasting changes in stereotypic-like behaviors in the open field test, although the latter study found that DMT reduced the duration of each episode of stereotypic activity. Similarly, repeated doses of DOI, TCB-2, or 25CN-NBOH did not induce lasting decreases in repetitive digging in the marble burying test in mice (Tsybko et al., 2020).

Two studies found that psychedelics produce lasting effects on alcohol consumption in mice. Alper et al. (2018) found that a single dose of LSD reduced alcohol preference and consumption in mice and that this effect lasted throughout the 46-day test period. In another study, TCB-2 significantly reduced alcohol consumption when tested in the 22 to 46-hour period after TCB-2 administration but did not affect saccharin preference (Kimmey et al., 2022). In the same study, a single dose of TCB-2 reversed the alcohol-induced deficit in chloride ion homeostasis in GABAergic neurons in the ventral tegmental area (Kimmey et al., 2022), a phenomenon related to continued consumption of alcohol (Kumar et al., 2009; Chester and Cunningham, 2002). In contrast to these findings, repeated high, moderate, or microdoses of psilocybin or two repeated high doses of LSD did not produce any lasting effects on relapse drinking in alcohol-habituated rats deprived of alcohol, although subchronic psilocybin produced a transient decrease in alcohol intake (Meinhardt et al., 2020). Similar lack of lasting effects on alcohol consumption was recently reported in mice treated with a single dose of LSD, despite using similar or higher doses than Alper et al. (2018) in the same mouse strain (Elsilä et al., 2022).

Using a series of conditioned place preference experiments in mice and rats, Vargas-Pérez et al. (2017) investigated the effects of 4-acetoxy-N,N-dimethyltryptamine (4-AcO-DMT), which is a prodrug of psilocin (Nichols and Frescas, 1999), on opiate and nicotine dependence. The aversive effects on place preference of both heroin withdrawal in rats and nicotine withdrawal in mice were blocked by 4-AcO-DMT. Furthermore, 4-AcO-DMT prevented conditioning to the rewarding effect of nicotine in mice when administered 24 hours before the first nicotine exposure. As drug dependence is suggested to switch the reward system to a dopamine-dependent motivational state (Vargas-Perez et al., 2009), the authors also investigated the rewarding effects of morphine administration in heroin-dependent rats receiving the $D_{1/2}R$ antagonist alpha-flupenthixol. The dopamine antagonist blocked the rewarding effects of morphine in heroin-dependent rats, and 4-AcO-DMT reinstated the rewarding effects of morphine in these rats despite coadministration with the dopamine antagonist, suggesting that $5\text{-HT}_{2A}R$ agonism may shift reward processing to a nondependent-like state (Vargas-Pérez et al., 2017).

In summary, psychedelics appear to have lasting effects on behaviors related to drug-dependence and addiction, but the studies are few and need to be substantiated. The effect of psychedelics on repetitive marble burying appears to be restricted to acute effects.

6. Cognition. A recent study assessed the effects of chronic treatment with DMT for 21 days on learning and memory in mice during the 10 days after the last dose (Morales-Garcia et al., 2020). In the Morris water maze, mice treated with DMT were quicker to escape to and spent more time on the target platform. Similarly, DMT-treated mice had shorter latency to explore and spent more time exploring the novel object in the novel object recognition test. Surprisingly, coadministration of the 5-HT_2R antagonist ritanserin did not abolish the behavioral effects of DMT, and the study found that the sigma-1 receptor antagonist BD1063, but not ritanserin, blocked the co-occurring hippocampal neurogenesis in vitro, suggesting a non-$5\text{-HT}_{2A}R$ mechanism for the lasting effects of DMT on learning (Morales-Garcia et al., 2020). In contrast, another study in mice administered repeated daily doses of DOI, TCB-2, or 25CN-NBOH after behavioral experiments to avoid drug exposure during behavioral assessment (Tsybko et al., 2020). The animals were tested in the Morris water maze for 5 days, and the authors did not find any effects of either compound on memory and learning, despite seeing changes in expression of brain-derived neurotrophic factor-related molecular markers (Tsybko et al., 2020). Similarly, Cameron and colleagues found no effects of repeated low doses of DMT on spatial working memory in rats, nor any significant effects of DMT on short-term memory in the novel object recognition test (Cameron et al., 2019). Another study also found no effects of DOI on novel object recognition in mice when tested 1 day after treatment (de la Fuente Revenga et al., 2021).

In summary, except for in one study using chronic doses of DMT, psychedelics do not appear to have lasting effects on different types of rodent cognition.

7. Social Interaction. One recent study found that repeated, but not single, administration of LSD promotes social interaction with a stranger in the mouse direct social interaction test 24 hours after the last dose and that there was a similar effect of repeated dosing on direct social interaction in rats. The authors similarly found lasting prosocial effects of repeated LSD in the mouse three chamber test (De Gregorio et al., 2021b). Repeated LSD administration in rats induced a similar prosocial effect by reducing the social distance in the open field test 1 month after the last LSD administration (King and Ellison, 1989).

In contrast to these reports, other studies report lasting antisocial effects. Chronic administration of LSD (every other day for more than 3 months) produced a lasting deficit in social behavior when assessed in a direct social interaction test 1 month after the last dose. LSD-treated rats were less social, more aggressive, and had increased levels of explorative sniffing of the opponent (Marona-Lewicka et al., 2011). A study in Syrian hamsters mirrors this effect. In animals that received TCB-2 during exposure to an empty cage, TCB-2 increased aggressive behavior toward a nonaggressive intruder 24 hours after administration and increased explorative sniffing of an aggressor confined to a closed-off section of a Y-maze 48 hours after administration (Clinard et al., 2015). Finally, Cameron and colleagues showed that repeated low doses of DMT did not alter interaction between rats in the three-chambered social approach paradigm (Cameron et al., 2019).

In summary, rodent studies of lasting effects on social behavior show inconsistent results.

Results from rodent behavioral studies investigating lasting effects of psychedelics across different behavioral domains emphasize the importance of choosing suitable time points for assessing behavior that translate to lasting clinical effects in humans. The results in this section suggest that the investigation of lasting effects of psychedelics on animal behavior is still at an early stage and that the effects are highly dependent on the experimental protocol.

IV. Perspectives on Animal Behavior in Psychedelic Research

A. Summary of Behavioral Effects

Psychedelic 5-HT_{2A}R agonists have a wide range of behavioral effects in laboratory animals. These compounds produce head twitches in mice that are highly predictive of psychedelic effects in humans (Halberstadt and Geyer, 2013a, 2018; Nichols, 2016; Halberstadt et al., 2020). Results from the drug discrimination test reveal that 5-HT_{2A}R agonists produce a unique profile of interoceptive cues that the animals can discriminate from other pharmacological effects (Fantegrossi et al., 2008; Hanks and González-Maeso, 2013; Nichols, 2016). Apart from these two main tests used to screen for 5-HT_{2A}R activation in vivo and predict psychedelic effects in humans, a plethora of studies have investigated the behavioral effects of psychedelics on behaviors that to some extent resemble human phenomenology. The objectives of these studies relate to both preclinical evaluation of psychedelics as medicines as well as basic understanding of 5-HT_{2A}R-mediated behavior. 5-HT_{2A}R agonists reliably inhibit sensorimotor gating in the PPI test during acute administration, especially in the rat, whereas studies in mice show conflicting results. Although tryptamine ligands acutely reduce locomotor activity in rodents, compounds of the phenethylamine class with much lower relative potency at the 5-HT_{1A}R increase gross motor activity, particularly at lower doses, but all classes appear to reduce other types of exploratory behavior or induce behavioral disorganization.

Acute administration of psychedelics to animals in tests related to anxiety-like behavior appears to be primarily anxiolytic-like, except for effects on central area exploration in the open field test. Effects in tests of depression-related behaviors reveal conflicting results, making it difficult to draw any clear conclusion on the effects of psychedelics in these tests. However, in tests of compulsive-like behaviors, 5-HT_{2A}R agonists show more consistent results, inhibiting different types of repetitive behaviors, including drug dependence-related behaviors. Although psychedelics appear to promote low-level classic conditioning and increase waiting impulsivity, studies on their effects in other domains of rodent cognition, like working memory and cognitive flexibility, as well as effects on rodent social interaction have shown discrepant results. Psychedelic-induced changes in time perception in rodents and the direction of such changes depends on the test schedule design, and the effects may be influenced by 5-HT_{2A}R-induced attention deficits.

Whereas most rodent studies investigate acute effects of the ligands, many studies within the past 5 years have focused on lasting effects to better reflect the lasting clinical effects observed in humans. However, like many of the acute effects, studies on lasting effects show conflicting results and appear to depend on the choice of species, strain, and protocol. Some of the questions that remain unanswered are: 1) which time point after drug cessation is most relevant when studying the behavioral response in rodents, and 2) which behavioral paradigm is best suited to study such an effect. Summaries of acute and lasting effects of psychedelics on rodent behavior in these behavioral domains are given in Tables 2 and 3, respectively.

B. Benefits and Challenges of Animal Behavior in Psychedelic Research

Animal experiments are quick to perform; it is possible to use new selective ligands not yet approved for clinical use; and the experiments can be coupled to ex vivo techniques, transgenic models, imaging, and electrophysiology, to name a few examples. Hence, despite the apparent challenges in translatability and reliability of the results, the use of animal behavior studies in psychedelic research remains indispensable. Although most current human studies use old ligands with well established safety profiles (Nutt et al., 2010), such as LSD and psilocybin (Nichols, 2016; Carhart-Harris and Goodwin, 2017; Johnson and Griffiths, 2017), these compounds are not necessarily the most optimal future drug candidates when considering both

therapeutic efficacy and long-term safety. For example, the active metabolite of psilocybin, psilocin, has ~20-fold higher binding affinity to the 5-HT_{2B}R compared with the 5-HT_{2A}R (Halberstadt and Geyer, 2011), and activation of 5-HT_{2B}Rs can potentially lead to heart valve disease (Rothman et al., 2000; Hutcheson et al., 2011). It is not known whether this translates to actual adverse effects in patients, especially if the compound is only used on one or two occasions in psychedelic-assisted psychotherapy (McClure-Begley and Roth, 2022), but might challenge the safety of microdose-type treatments where users self-administer low, subpsychedelic doses several times weekly (Lea et al., 2020). Using animal behavioral tests in psychedelic drug development in the search of new drug candidates or to better understand the existing ones therefore remains an important aspect of psychedelic research.

Based on the present review, the HTR test is currently the most reliable behavioral tool in psychedelic drug development. It can be used as an in vivo screening test to confirm 5-HT_{2A}R activation previously detected in in vitro studies, to test whether the compound reaches the target site in the brain, and to predict whether a new compound will be psychedelic in humans. As psychedelic-elicited mystical experiences in humans have been shown to correlate to clinical efficacy (Garcia-Romeu et al., 2014; Barrett and Griffiths, 2018; Roseman et al., 2018), and head twitches in mice predict psychedelic effects in humans (Halberstadt et al., 2020), it is tempting to extrapolate that the proxy measure of head twitches in rodents can also predict clinical efficacy in humans. However, the HTR test has low face validity to human responses to psychedelics, and it is not yet known whether the psychedelic experience is necessary for the clinical effect or simply an epiphenomenon (Olson, 2020; Vollenweider and Preller, 2020; McClure-Begley and Roth, 2022). Human psychology is complex, and the efficacy of psychedelics in treating mental illness relies not only on the intensity of the experience but also on the quality of it (Roseman et al., 2018). A recent study indicated that a long list of non-5-HT_{2A}R targets modulate the subjective psychedelic experience based on language analysis of recreational user reports (Ballentine et al., 2022). Furthermore, non-5-HT_{2A}R effects of psychedelics, such as 5-HT_{1A}R-mediated dampening of the limbic system (Nichols, 2016; Carhart-Harris and Nutt, 2017), may hypothetically modulate the subjective experience in favorable ways, and some rodent studies support the theory of non-5-HT_{2A}R-mechanisms of psychedelics that could promote therapeutic action (Cameron et al., 2019; Morales-Garcia et al., 2020; Hesselgrave et al., 2021). Animal behavioral tests predictive of the clinical utility of new psychedelics in humans remain to be established. Studies on lasting effects of psychedelics in rodents are still few, especially studies that assess behavior past a weekly washout period. The lasting effect of psychedelics observed in clinical studies (Johnson et al., 2014; Bogenschutz et al., 2015; Gasser et al., 2015; Carhart-Harris et al., 2018) warrants a paradigm shift in how drug effects are examined in humans and animals. Traditionally, pharmacology studies in animals are designed to examine immediate effects, i.e., while the compound is still in the body. Perhaps it is also difficult to show these long lasting effects in rodents, and the lack of long-term data might partly represent a publication bias (Ioannidis, 2005). The acute studies can tell us how 5-HT_{2A}Rs modulate behavior, helping us understand the link between receptor activation, behavior, and the acute psychedelic state, but do not necessarily predict clinical effects. Examining the acute effects of 5-HT_{2A}R agonists in e.g., standard tests predictive of antidepressant or anxiolytic effects, such as FST and EPM tests, may therefore not be useful from the drug development perspective. These tests are biased toward having predictive validity for antidepressant and anxiolytic drugs with certain pharmacological profiles (Campos et al., 2013; Gururajan et al., 2019) while the animal is still under the influence of the drug. Although such conventional tests are useful for high-throughput preclinical screening of drug candidates that patients take daily, their conventional use may not be as suitable for studies pertaining to psychedelic-assisted psychotherapy, where the effect of the drug lasts well past the pharmacokinetic elimination profile (Johnson et al., 2014; Bogenschutz et al., 2015; Gasser et al., 2015; Carhart-Harris et al., 2018).

C. Future Perspectives for Animal Behavior in Psychedelic Research

Animal behavioral experiments that go beyond the simple conventional depression and anxiety tests would improve the predictive value of animal behavioral experiments in preclinical psychedelic research. In general, as proposed as part of the Research Domain Criteria (RDoC) initiative, it would improve mental health research not to focus on limited clinical diagnoses but on psychiatric symptoms that span a wide range of illnesses (Insel et al., 2010). Indeed, the transdiagnostic potential is a unique feature of psychedelic-assisted psychotherapy (Kočárová et al., 2021). Kelly and colleagues recently reviewed the transdiagnostic effects of psychedelics within the RDoC framework and highlight that implementation of the RDoC framework in psychedelic research will bridge the translational gap between preclinical neuroscience and clinical studies (Kelly et al., 2021). Apart from finding the appropriate behavioral tests, we should also continue looking for appropriate time points after drug administration. Studies designed to encompass both acute and lasting effects of psychedelics would

certainly strengthen our understanding of the time course of changes in animal behavior. As evident from the studies reported in this review, results often contradict each other and are highly dependent on changes in protocol. Following ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines will improve the reporting of results and chances of replication of behavioral effects of psychedelics across laboratories and help elucidate the experimental conditions critical for the behavioral effects of psychedelics in laboratory animals (Percie du Sert et al., 2020). In addition, publication bias may be a considerable factor, as negative results are often not published. Identifying animal behaviors that are most translatable to the clinical situation and coupling these behaviors to fingerprint alternations of molecular markers (Martin and Nichols, 2018; de la Fuente Revenga et al., 2021), electrophysiology (González-Maeso et al., 2007), and imaging studies (Shao et al., 2021) that also translate to clinical efficacy in humans would be the ultimate goal in animal psychedelic research.

V. Strengths and Limitations of This Review

This review focused on animal behavior, but there are many other ways to evaluate the effects of 5-HT_{2A}R agonists in animals (González-Maeso et al., 2007; Ly et al., 2018; Martin and Nichols, 2018; Shao et al., 2021). Coupling these techniques to behavioral readouts strengthens the utility of the behavioral tests described in this review. We have included many different behaviors of relevance to both mechanistic understanding of 5-HT_{2A}R biology and preclinical studies of psychedelics as medicines. Our search uncovered contradictory results and null results, and all identified studies are presented in an unbiased manner. It is still not known how other targets of psychedelics than 5-HT_{2A}R contribute to the potential therapeutic effects of psychedelics (Nichols, 2016; Vollenweider and Preller, 2020), or which downstream signaling pathways of 5-HT_{2A}R activation are necessary for the therapeutic effect (Urban et al., 2007; Nichols, 2016; McClure-Begley and Roth, 2022). We therefore did not exclude any psychedelic 5-HT_{2A}R agonists from this review. However, studies in which it was unclear whether the effect related to the active psychedelic compound were excluded. We therefore excluded a study that showed efficacy of psilocybin but no effect of psilocin (Sard et al., 2005) and a study on ayahuasca, which contains a monoamine oxidase inhibitor that in itself can affect behavior (Pic-Taylor et al., 2015). Activation of other receptors than the 5-HT_{2A}R could in theory contribute to clinical efficacy of psychedelics, and a few recent rodent studies support this theory (Morales-Garcia et al., 2020; Hesselgrave et al., 2021). Although most clinical studies use psilocybin or LSD, the reader may have noticed that many of the preclinical studies cited in this review use phenethylamines like DOI or 25CN-NBOH, a discrepancy that could partly explain the obvious translational gap. Most of the included studies used rats and mice, as they are the most commonly used laboratory animals, but we also included results from rabbits, hamsters, and zebrafish where applicable. Finally, as previous reviews have extensively covered the HTR, drug discrimination, PPI, and locomotor activity tests (Fantegrossi et al., 2008; Halberstadt and Geyer, 2013b, 2018; Nichols, 2016), we decided to limit the sections about these behaviors to main points.

VI. Conclusion

Studies of animal behavior can contribute to psychedelic research by aiding the understanding of how 5-HT_{2A}Rs modulate behavior and supporting preclinical drug development of second-generation psychedelics. However, the behavioral tests we normally use to study psychiatric symptom domains show inconsistent results with psychedelics, and the acute effects of psychedelics in such tests are of questionable translational validity to clinical efficacy in humans. Investigating psychedelics in tests related to transdiagnostic symptom domains, such as cognitive and social effects of psychedelics, studying behavior after the elimination of the drug from the bloodstream, and publishing negative findings will improve the use of animal behavior in psychedelic research.

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