Classic Psychedelics in Translational Research: Addressing Epistemic Challenges from Bench to Bedside

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**Abstract**

In the last decade alone, a growing body of preliminary evidence suggests that classic psychedelics (CPs) can rapidly and durably ameliorate symptoms and cognitive deficits associated with depression. However, the mechanisms by which CPs work in the brain are not well understood. Rodent translational research, in which experimental findings from rodents are translated to humans, is fundamental in achieving this goal. This chapter focuses on a representative subset of human and rodent studies investigating CPs for depression, including the various lines of research that have been initiated to understand how they work. Our aim is to show that in addition to epistemic challenges that scientists face in translating findings from rodents to humans, there is also mismatch between experimental approaches used to investigate CPs in humans and rodents. We thus show current experimental practices are not conducive to mechanistic discovery. We end with a set of positive proposals to expedite the drive to translate CPs into effective treatments for depression.

*Keywords*: classic psychedelics, psychiatry, clinical trials, collaboration, extrapolation, major depressive disorder, open science, philosophy of science, rodent models, scientific practice, translation, validity

**1.0. Introduction**

According to the World Health Organization, depression, or *Major Depressive Disorder* (MDD) “is the leading cause of disability worldwide and a major contributor to the overall global burden of disease” with an estimated “5% of adults” globally suffering from it. Although this estimate is surprising given the availability of anti-depressants (e.g., selective serotonin reuptake inhibitors), pharmacological research has not yet advanced treatments to adequately meet clinical need. Existing treatments do not result in remission of symptoms in all persons suffering from depression and even when they are efficacious, relief comes after weeks to months of use, with symptom remission often accompanied by negative side effects (e.g., weight gain/loss, sexual dysfunction). Commercially available anti-depressants also must be taken daily for extended periods, if not an individual’s lifetime, and cessation of treatment, or gradual titration down of dose may result in “rebound” effects accompanied by prominent recurrence of depressive symptoms and higher risk of suicidal ideation. For these reasons, scientists seek alternative interventions with potentially higher response rates and without adverse effects.

Classic psychedelics (CPs) are a class of hallucinogens—including, LSD, psilocybin, mescaline, and DMT—primarily known as serotonin-2a (5-HT2A) receptor agonists.[[2]](#footnote-2) In the last decade, findings from small-scale clinical trials suggest CPs can rapidly and durably ameliorate symptoms and cognitive deficits associated with MDD and treatment-resistant depression (TRD). The use of neuroimaging in these studies also have begun to shed light on how a subset of SPs act in the brain to produce their therapeutic effects. (e.g., Carhart-Harris et al., 2018; Davis et al., 2021). A key driver of this research is the ‘psychedelic experience’—an altered state of consciousness described as being ‘mystical’ or ‘spiritual’. Psychometric assessments using the Mystical Experience Questionnaire (MEQ30), 5- or 11-Dimensional Altered States of Consciousness Questionnaire (5D- or 11D-ASC), and the Hallucinogen Rating Scale (HRS), have provide some insight into what aspects of these phenomenological experiences are potentially therapeutic and transformative in nature. Moderate-to-high doses of CPs evoke characteristic experiences including, spiritual encounters, transcendence of space and time, and new psychological insights about the self and others.

These exciting preliminary findings have rapidly and globally instigated many independent lines of basic research using rodent models of depression to determine the mechanisms by which CPs bring about their therapeutic effects. However, while the rise in psychedelics research over the past decade has been rapid, progress to date in understanding the brain mechanisms by which these drugs work has been slow. In this chapter we argue that this is due not only to the kinds of epistemic challenges that psychedelics researchers working with human clinical populations and rodent models of depression confront, but also a current lack of synchronization across research groups to address these epistemic challenges. We make the case that a shift from independent research groups working out of synch to the development of structured research communities who coordinate research practices and share knowledge, methods, and data openly, is key to accelerating future translational research.

We begin in Section 2, by briefly describing the iterative structure of CP research whereby findings from clinical and neuroimaging research on humans with depression informs mechanistic research on rodent models of depression, and findings from these studies shapes understanding of the mechanisms by which these drugs work in humans. In Section 3, we review a set of representative clinical and neuroimaging studies investigating the efficacy of psychedelics for depression, including various lines of research that have been initiated to understand how they work. Despite their promising results, idiosyncratic features of study designs and methodologies lead to challenges in using these findings to ground mechanistic research in rodent models. Additionally, as we explain in Section 4, research on rodent models of depression is plagued by lack of agreement across research teams with respect to the best investigative strategies for studying the mechanisms by which CPs bring about positive therapeutic effects. Given the great promise that CPs hold for treating depression and other mental illnesses, we put forward a set of positive proposals in Section 5 to accelerate the drive to translate CPs into effective treatments for depression.

**2.0. Preclinical & Clinical Research & the Goals of Translation**

As we explain in Section 3, only a handful of preliminary clinical and neuroimaging studies to date have sought to investigate the effects of CPs on the brain and on symptoms associated with depression. These small-scale exploratory studies with members of clinical populations have shown great promise that, given the right dosage and setting, CPs may effectively alleviate MDD and/or TRD symptoms. Neuroimaging studies, while shedding light on brain areas involved in mediating CPs’ therapeutic effects, provide little insight into cellular and molecular mechanisms by which these effects come about. Behavioural and intervention experiments in rodents are thus key to mechanistic discovery.

In contrast to clinical researchers, rodent behavioural researchers are engaged in translational research (e.g., de Gregorio et al. 2021). This involves both backward and forward translational work (e.g., Hvoslef-Eide et al. 2016). First, they must make decisions about how best to model depression in rodents based on current understandings of mental illness in humans. They also rely on findings from clinical and neuroimaging studies to determine where in the brain to direct their interventions to determine if CPs ameliorate depressive-like symptoms in rodents and by what mechanisms. They also are engaged in *forward translational research;* they intend mechanistic findings from rodent studies to tell them something about the mechanisms by which CPs work in humans.

Given that we are interested in pinpointing steps in this iterative process where decisions are made that may impede progress in CP research and stall treatment development, our aim in this section is simply to sketch the basic steps from clinical and neuroimaging studies to rodent studies and back.

            Researchers conducting preliminary clinical studies like those we describe in Section 3 might recruit human subjects based on satisfaction of DSM diagnostic criteria for MDD or scores on associated clinician-administered depression rating scales, such as the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Åsberg Depression Rating Scale (MADRS). The DSM-5 operationally defines MDD as involving either (1) “depressed mood” and/or (2) “loss of interest or pleasure”, that persists for at least a 2-week period and that is accompanied by four or more of the following symptoms: “significant non-diet related weight and/or appetite loss”, “insomnia”, “psychomotor agitation”, “fatigue”, “feelings of worthlessness/inappropriate guilt”, “diminished ability to think or concentrate” or “lack of decisiveness”, and “suicidal ideation”. Additionally, the symptoms must “cause significant distress or impairment in social, occupational, or other important areas of functioning” and not be “attributable to the physiological effects of a substance or to another medical condition” (American Psychiatric Association [APA], 2013, 160-161). Just as the DSM diagnostic criteria may inform recruitment of human subjects into clinical studies, they may also serve to impact decisions that rodent behavioural researchers make in developing and/or selecting rodent models of depression to be used in SP research.

A starting point for a study might be to operationally define MDD based on all or just some of the above-mentioned DSM-5 diagnostic criteria. This choice not only informs recruitment of subjects but also impacts other methodological decisions researchers must make to effectively measure the effects of psychedelics on MDD. In considering factors like heterogeneity and comorbidity across study populations, researchers might adopt criteria that exclude psychological conditions such as a history of mania/hypomania and other psychiatric diagnoses that may increase the risk of adverse outcomes or impede the success of the study. Minimizing variation at the recruitment stage is one strategy researchers use to reduce potential confounds to establishing a causal relationship between a treatment and observed behavioural effects. Additionally, they must consider factors that might impact the internal and external validity of clinical trials such as the type of study design (e.g., open label, randomized, placebo-controlled), exclusion/inclusion criteria, and type of assessment tools/instruments used.

Rodent translational research is often shaped by some of the same but also different epistemic benchmarks, and collaborations between pre-clinical rodent behavioural researchers and clinical researchers and cognitive neuroscientists is uncommon (e.g., Sullivan et al. 2021). With respect to CPs and depression, translational scientists aim to identify the neural mechanisms by which CPs act on the brain and impact behaviour in rodent models of depression and then extrapolate those findings to humans. Extrapolation is associated with the aim of *external validity*; researchers working with rodent models of depression aim to arrive at causal claims in the laboratory about CPs and depression that will apply to members of the human population who suffer from MDD or TRD. These aims may dictate the selection of rodent models of depression based on what aspect of depression they induce and their applicability to MDD or TRD, the choice of drug, dosage and treatment regimen, and the specification of behaviours that will be taken as indicative of the success of the intervention. Researchers, however, may have different perspectives about what kind of knowledge they want to extrapolate and the best strategy for attaining that kind of knowledge. They may aim for experimental conditions favourable to create a depressed rodent with specific features of depression, or a depressed rodent resistant to available anti-depressant therapies, thus aiming for *construct validity* of the rodent model. The rationale for favouring construct validity is that if the same phenomenon under study in the human (i.e., MDD, TRD) is under study in the rodent model, then findings testing the therapeutic efficacy of psychedelics in that model will better translate to humans with MDD or TRD. Also, if a rodent model of depression is construct valid, it may be taken to indicate that the same/similar brain structures that are implicated in MDD or TRD also will be implicated/impacted in the rodent model (i.e., *neurocognitive validity*). If the same structures are impacted, using that rodent model to determine the anti-depressant efficacy of a CP may shed light on the neural mechanisms by which CPs work in humans with depression. Alternatively, researchers may aim to achieve *predictive validity* in developing a rodent model. In this case, they may want to know if a CP will work in a rodent model of depression and use their findings as a basis for predicting whether it will work in humans. They also may simply be interested in predicting the kinds of circuit, cellular and molecular level events that may happen downstream of the intervention. Predictive validity on its own may reveal the potential therapeutic efficacy of a drug; it is not, however, sufficient for understanding how these drugs act on the brain and the kinds of changes they initiate (e.g., synaptic plasticity) that may give rise to their beneficial effects.

With these basic distinctions in mind, in the next two sections we describe and evaluate recent clinical and neuroimaging studies on CPs (Section 3) and recent rodent behavioural research (Section 4) targeted at mechanistic discovery.

**3.0. Clinical and neuroimaging studies**

Clinicians and researchers have been interested in the therapeutic potential of CPs since their introduction to Western psychiatry in the early 1950s, given their utility as an adjunct to psychotherapy (e.g., Carhart-Harris et al., 2015). Despite holding much promise, prohibitive laws stalled research around 1965, until a recurrence of studies in the 1990s (e.g., dos Santos et al, 2016) unfolded into the revival of scientific interest today. Today, an abundance of clinical (e.g., Carhart-Harris et al., 2015; Griffiths et al., 2011; Grob et al., 2011; Moreno et al., 2006; Schmid et al., 2015) and neuroimaging (e.g., Carhart-Harris et al., 2012, 2016b; Riba et al., 2004) studies have laid the groundwork for research on CPs in depression. In this section, we provide an overview of three research groups that have conducted studies exclusively on CPs in MDD and TRD, to date, including the tools used to assess depressive symptoms, CP-induced subjective phenomenological experiences, and the impact of CPs on the brain. Our aim is to show idiosyncratic features of study design and methodologies that impede the generalizability of results and lead to challenges in using findings to ground mechanistic research in rodents. Additionally, apart from common study limitations (e.g., small sample size, no control or placebo group) we point to some distinct limitations that restrict the interpretation of findings.

The earliest clinical trials come from Osório and colleagues, who sought to investigate the short-term effects of a single dose of ayahuasca (AYA) tea, a traditional Amazonian beverage containing DMT, in participants with a DSM-5 diagnosis of depression.[[3]](#footnote-3) In their first study on MDD, after determining baseline scores representing depression severity using the HAM-D, participants received 2mL/kg AYA. Frequent evaluations showed that scores for “typical” MDD symptoms were reduced after just 40 minutes—approximately when the psychedelic effects of AYA take effect—and sustained for 28 days (Osório et al., 2011).[[4]](#footnote-4),[[5]](#footnote-5) In another study (Osório et al., 2015) (120-200 mL AYA, 2.2 mL/kg), weekly MADRS assessments revealed a significant improvement in depressive severity after 21 days.[[6]](#footnote-6) Lastly, in a placebo-controlled study, Osório and colleagues found that after 7 days depression severity (MADRS) was significantly reduced in the AYA group (1mL/kg) compared to the placebo group; but more noteworthy is that a considerably large placebo was reported, undermining the efficacy of AYA (Palhano-Fontes et al., 2019). However, it was assumed this was the result of a “care effect” since the study occurred in a comfortable and supportive environment and higher placebo responses were observed in participants living with “significant psychosocial stressors.”[[7]](#footnote-7) Furthermore, they note that previous research indicates higher placebo responses in participants with low socioeconomic status and comorbid personality disorder, which was the case in their study. While these explanations are plausible, strong placebo responses were more likely due to ‘expectancy effects’ considering participants were all Brazilian and the study took place in Brazil, where there is a longstanding history of AYA use among several Amazonian religions.[[8]](#footnote-8) To better extrapolate findings to the clinical population at large, recruitment strategies should be developed to include participants from diverse ethnic and socioeconomic backgrounds.

In any case, the two remaining research groups have focused on psilocybin-assisted therapy (PAT), since earlier research suggests psilocybin may elicit long-term positive psychological and behavioural changes by enhancing psychotherapeutic processes (Carhart-Harris et al., 2012; Griffiths et al., 2011; Grob et al., 2011; Moreno et al., 2006). Carhart-Harris and colleagues investigated PAT in TRD in participants with “major depression of a moderate to severe degree” satisfied by a HAM-D score of ≥17 (Carhart-Harris et al., 2016a, 620).[[9]](#footnote-9),[[10]](#footnote-10) They also opted to use the Inventory of Depressive Symptomatology Self-Rating Scale (QIDS-SR16) “due to its brevity, increasingly widespread use, and validity at 1 week intervals” (622). Participants underwent PAT twice, a week apart, with two doses (session 1: 10mg; session 2: 25mg) administered as 5mg capsules (Carhart-Harris et al., 2016a, 2018). Short-term assessments indicated that depression severity significantly improved after 5 weeks and 3 months post-25mg dose (Carhart-Harris et al., 2016a) and assessments made during a 6-month follow-up study revealed that reduced QIDS-SR16 scores sustained long-term (Carhart-Harris et al., 2018).

The same group compared the efficacy between psilocybin and escitalopram in MDD (≥17 on HAM-D) (Carhart-Harris et al. 2021). Participants were randomly allocated into a ‘psilocybin group’ or ‘escitalopram group’ and both received psychological support. In the first group, two separate doses of 25mg psilocybin were administered, 3 weeks apart, followed by a daily placebo for 6 weeks. The escitalopram group received two doses of 1mg psilocybin, administered 3 weeks apart, followed by 10mg escitalopram daily. After 6 weeks, QIDS-SR16 scores revealed no significant difference between the efficacy of the two treatments. Although it was proposed that psychological support may have improved outcomes in the escitalopram group, results were more likely confounded by expectancy effects given that ‘previous use of psilocybin’ was not excluded during the recruitment stage “…and many expressed a preference for psilocybin over escitalopram” (1410).

The most recent clinical trial comes from Davis and colleagues. They investigated PAT in MDD (DSM-5 and ≥17 on GRID-HAMD) using the GRID-HAMD as a primary outcome measure due to its “high validity and reliability” (Davis et al., 2021).[[11]](#footnote-11),[[12]](#footnote-12) One aim was to “differentiate the psilocybin intervention from spontaneous symptom improvement” (483) and to control this, participants were randomly assigned to receive treatment either immediately (immediate group) or 8 weeks after enrolment (delayed group). Participants underwent PAT twice, a week apart, with two separate doses of psilocybin administered as one capsule (25mg/70kg; session 2: 30mg/70kg). One month after the second PAT session, they found a treatment response and remission rate of 71% and 58%, respectively, across all participants, and reductions in depression severity persisted up to 6 months. Lastly, in a 12-month follow-up GRID-HAMD scores revealed a response rate of 75% and a sustained remission rate of 58% (Gukasyan et al., 2022).

Despite these studies yielding important findings, idiosyncratic features in study design raises concerns about how these findings fit together to lay the groundwork for future research. The most obvious is variation in CP type, dosage, and administration. Although AYA and psilocybin show some similarity in their effects, it is difficult to assume they have identical downstream effects. For instance, AYA contains harmine, harmaline, and tetrahydroharmine—chemically distinct compounds known to have anti-depressant properties and research suggests that the psychedelic effects of AYA occur via combined interaction between harmine and DMT.[[13]](#footnote-13),[[14]](#footnote-14) Without appropriate measures, how can researchers attribute the effects of AYA to DMT alone? This also raises questions about the implications of different dosages and modes of administration and moreover, participant’s use of other medication, since little is known about whether they have lasting effects and thus, confounding influences.[[15]](#footnote-15)

Idiosyncratic features are also found within the inclusion/exclusion criteria. One of the first decisions clinical researchers must make is define features prospective participants must have if they are to be recruited for a study, and these features are what investigators use to answer their research question. While we cannot detail every inconsistency between these studies their diversity is important to mention because it suggests there are conflicting views about how inclusion/exclusion criteria should be operationalized. We made note of which studies operationally defined depression based on the DSM-5 diagnostic criteria or scores on associated depression rating scales (HAM-D and QIDS-SR16). Yet are these approaches interchangeable? The HAM-D evaluates the degree to which ‘items’ associated with depression are experienced in the past week, excludes anhedonia, and was designed to determine depression severity (mild, moderate, severe) (Hamilton, 1960). It is unlikely for example, that the DSM-5 correlates to depression severity since it only determines whether someone has a depressive disorder. Moreover, the DSM-5 considers symptoms experienced in the last 2 weeks, and depressed mood or anhedonia is a requisite criterion. Even if research groups standardize how depression is operationalized, heterogeneity across study populations will remain. In one AYA study alone some participants were diagnosed with an anxiety disorder and comorbid personality disorder was high (Palhantos-Fontes et al., 2019).Typically, researchers aim to reduce heterogeneity to improve the generalizability of finding (external validity); yet with different rationales behind the implementation of inclusion/exclusion criteria, external validity is limited.

Moving forward to methodologies, we so far illustrated the different depression rating-scales used to measure the efficacy of CPs. Efficacy is generally operationalized as ‘the differences in participant’s final scores versus baseline scores, expressed a standard effect size.’ It is the depression rating scales that vary in the constructs (e.g., feelings of guilt, pessimistic thoughts) they are designed to measure. This is a bit of a caveat since researchers must be cautious in choosing rating scales that actually measure the constructs they intend to measure (construct validity) so as to avoid making conclusions based on biased data. In the study comparing psilocybin and escitalopram (Carhart-Harris et al., 2021), the primary outcome measure (QIDS-SR16) did not reveal a significant difference between the two treatments but secondary outcome measures “favoured psilocybin.” This raises concerns about the validity of these scales and their usefulness in discriminating between different treatments. Given that little is known about how different depression rating scales correlate, especially between self-rating and clinically administered scales, it is an interesting question as to how the data collected from these scales fit together in a way that can be extrapolated for future research.

Similar issues arise with psychometric scales used to measure subjective psychedelic experiences. In one study, Osório and colleagues sought to determine whether specific aspects of the hallucinogenic and mystical effects induced by AYA correlated with therapeutic outcome, using the HRS and MEQ30, respectively (Palhanos-Fontes et al., 2019). Overall scores were not predictive of positive clinical outcome, however, the study revealed strong correlations between reduced MADRS scores and the MEQ30 factor ‘transcendence of time and space’ and HRS subscale ‘perception’.[[16]](#footnote-16) Since some participants with increased scores in ‘perception’ did not show positive clinical outcome, these findings were interpreted to suggest that mystical effects rather than hallucinogenic effects are more pertinent to clinical outcome.

Carhart-Harris and colleagues hypothesized that the 11D-ASC subscales, ‘insightfulness’, ‘experience of unity’, ‘spiritual experience’, and ‘blissful state’, would be predictive of long-term clinical outcome (Carhart-Harris et al., 2018).[[17]](#footnote-17) To test this, they assessed participant’s 11D-ASC scores from the second PAT session alongside their QIDS-SR16 scores collected 5 weeks after, and the study revealed a significant correlation between the three subscales and improvements in depressive severity. They tested a similar hypothesis in a supplementary study using the 5D-ASC because it measures a broader range of subjective phenomena, compared to the MEQ30. This permitted them “to test the specificity of the relationship between mystical-type experiences (vs. e.g., perceptual changes) and subsequent therapeutic outcomes” (Roseman et al., 2018b, 2). Their study revealed that the dimension ‘oceanic boundlessness’ correlated more strongly with positive clinical outcome, while altered visual and auditory perceptions correlated less.

What is most interesting is that Davis and colleagues have reported a much different conclusion about mystical experiences. While MEQ30 scores from both PAT sessions were predictive of positive clinical outcome after 4 weeks, there was no correlation between improvements in depressive symptoms observed after 3-,6-, and 12-months (Gukasyan et al., 2022). Two explanations were offered (1) that the study was underpowered to detect such a correlation or (2) “this difference may reflect a lack of such relationship in a sample of individuals with MDD as opposed to depressive symptoms secondary to a cancer diagnosis” (156).

Taken together, these findings show that the therapeutic efficacy of the psychedelic experience is unclear. These rating scales also differ in the scope of constructs they measure, and they pose the same challenges we laid out with respect to the validity of depression rating scales. Yet, despite these variations influencing the discrepancy between findings, it is more likely that the scores were confounded by different doses of CPs.

In the last part of this section, we describe different neuroimaging techniques employed across studies to investigate the impact of CPs on different brain regions. Osório and colleagues used single photon emission tomography (SPECT) to determine the effects of AYA on regional cerebral blood flow (rCBF), 8 hours after consumption (Sanches et al, 2016). The observed changes were increased rCBF in the left nucleus accumbens, right insula and left subgenual area—brain regions implicated in regulation of mood and emotions.

Carhart-Harris and colleagues carried out multiple studies using functional magnetic resonance imaging (fMRI) to investigate the effects of psilocybin, a day after the second PAT session (Carhart-Harris et al., 2017). Findings revealed decreased amygdala CBF and increased resting-state functional connectivity (RSFC) within the default mode network (DMN), a higher-order brain network implicated in self-representation and introspection. Increases in RSFC between the ventromedial prefrontal cortex (vmPFC) and the bilateral inferior-lateral parietal cortex (ilPC) nodes of the DMN and decreases in RSFC between the bilateral parahippocampal (PH) and PFC, were predictive of treatment response. In investigating whether specific aspects of mystical experiences were predictive of changes in PH RSFC, a post-hoc analysis revealed that participants with the highest scores on the 5D-ASC dimension ‘oceanic boundlessness’ “had the greatest decreases in PH RSFC in limbic…and DMN-related cortical regions” (4).[[18]](#footnote-18) Lastly, fMRI data collected during an *emotional face paradigm*, revealed increased response in the right amygdala to fearful and happy faces (Roseman et al., 2018a). Improved facial recognition was linked to decreased RFC between the amygdala and PFC, and this was predictive of treatment response (see Mertens et al., 2022; Stroud et al, 2018). These findings were interpreted to suggest that PAT mediates long-term improvements in emotional processing, by enabling participants to fully engage with negative emotions (Mertens et al., 2022).

Davis and colleagues collected fMRI data a week after the second PAT session instead. They also investigated the effects of psilocybin on cognitive flexibility using a *set-shifting task* (Doss et al., 2021). Psilocybin was found to improve cognitive flexibility for up to 4 weeks. Notably, fMRI data revealed increased dynamic functional connectivity (dFC) between the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), but by the 4-week point, increases in ACC-PCC dFC did not correlate with improvements in cognitive flexibility. They provided two possible explanations, that cognitive flexibility might not be mechanistically related to the therapeutic effects of psilocybin, or the GRID-HAMD might not assess cognitive impairments associated with depression.

**4.0. Rodent Translational Research & Classic Psychedelics**

Although the focus of this section is rodent behavioural research on CPs undertaken during the past two decades, at least since the 1970s researchers have been interested in the anti-depressant potential of these compounds, given their ability to modulate serotonergic neurotransmission, which has been implicated in the processing of emotional states, learning, memory, and attention (e.g., Harvey, 2003). Findings from clinical studies like those described in the previous section have ushered in a new era of rodent behavioural research directed at understanding the impact of CPs on the brain and behaviour and the mechanisms by which they bring about their purported therapeutic effects. While rodent studies have included research to investigate the impact of CPs on serotonin receptors and cellular and molecular mechanisms thought to mediate synaptic plasticity (e.g., AMPA receptor trafficking; second messenger signalling cascades) (e.g., Vollenweider & Kometer 2010; Jaster et al. 2021), in this section we focus on research directed at understanding the impact of CPs on rodent models of depression.

One of the first decisions that researchers working with rodents must make is which model of depression to use to assess the effects of CPs. They might use a particular experimental paradigm/procedure to produce depressed mice, a rodent strain that has a depressive-like phenotype, or a knock-out mouse model of depression (e.g., Scherma et al. 2019). To date, it has been common for CP researchers to use experimental procedures to produce rodent models of depression rather than use knock-out mice.

The most widely used experimental paradigm for producing a depressed rodent is the *Forced Swim Task* (FST). Roger Porsolt (1977, 1978) originally developed this “test of behavioural despair” to assess the efficacy of serotonergic anti-depressants. In the FST, rats or mice are submerged in a cylindrical tank of clear water deep enough that their feet and tail cannot touch the bottom. Wildtype rodents initially will attempt to escape by paddling vigorously, but they eventually give up, adopt an immobile posture, and passively float with their head just above the water’s surface. The period of immobility after an attempt to escape is taken to indicate “behavioural despair”, and any treatment that leads to a reduction in this immobility period is interpreted as having anti-depressant like effects.

In one of the earliest studies to assess antidepressant efficacy of CPs (Górka et al.1979), adult male Wistar rats were injected intraperitoneally (i.p.) with 0.5 and 1.0 mg/kg doses of LSD prior to being placed in the FST. Researchers found that LSD not only failed to significantly reduce immobility time—it slightly *increased* it. In contrast, a recent study (Cameron et al. 2018) investigated the impact of three temporally spaced 10mg/kg doses of DMT (primary compound in ayahuasca) on immobility duration in male Sprague-Dawley rats in the FST[[19]](#footnote-19), and found that rats exhibited decreased immobility time, increased swimming time but equal climbing time compared to controls. This same research group (Cameron et al. 2019), seeking to mimic human psychedelic micro-dosing, gave chronic intermittent doses of DMT in smaller concentrations (1mg/kg) to male and female Sprague-Dawley rats every 3rd day during a 2-month period. Given statistically significant reductions in immobility and increases in swimming and climbing times in DMT treated animals compared to controls when tested in the FST, the researchers concluded that DMT micro-dosing has antidepressant effects. Another study (Hibicke et al., 2020) sought to determine whether psilocybin and LSD compared to ketamine “alleviated depressive-like symptoms and anxiety in a rat model for depression”. They divided 9-15 weeks old male Wistar Kyoto rats into four groups: (1) saline, (2) psilocybin (1.0mg/kg), (3) LSD (0.15 mg/kg), or (4) ketamine (5.0, 20, or 100 mg/kg dissolved in vehicle). They found that psilocybin and LSD treated rats were less immobile than controls and significantly more likely to swim and climb in the FST than saline treated rats.

Despite its widespread use, there is uncertainty in the rodent behavioural literature as to what the FST actually measures—whether the duration of immobility is a depression-like behaviour or a stress-coping strategy (e.g., Commons et al. 2017). Using the FST alone to assess the effects of CPs exclusively on depression is thus problematic, which is likely why some research groups combine its use with other experimental paradigms for assessing depression. Given co-morbidity between DSM categories of depression and anxiety, a case could be made that Hibicke and colleagues were justified in using the Kyoto-Wistar rat strain in the FST due to greater “face validity”—these rats look more similar to their human-like counterparts who present with depression and anxiety. Yet, what are investigators trying to model using the FST? It is not a valid model of MDD, which is an *enduring* condition. The FST also is not a valid model of TRD; it is used as a test of anti-depressant efficacy and other commercially available drugs that have led to reduced immobility in the FST and which are now commercially available are not effective in treating TRD. So, it is not clear what new knowledge can be gained about the efficacy of CPs in treating TRD using the FST alone. This is perhaps why some researchers elect to use a testing battery including the FST and other behavioural measures (e.g., elevated plus maze, fear conditioning) to determine a broader phenotypic profile for rodents treated with CPs. Other researchers who want a more construct valid rodent model of human depression opt instead to use other rodent models.

This is in fact the strategy used by Tobias Buchborn and colleagues (2014), who assume that because human depression is a persistent condition that generally responds to repeated use of anti-depressants, it is preferable to use a rodent model that is relevant to the clinical condition. To develop such a model, they (Buchborn et al. 2014) bilaterally removed the olfactory bulbs of 7-week-old male Wistar rats, a procedure previously used to test the efficacy of other anti-depressants (e.g., Jesberger & Richardson 1986). Following this procedure, rats exhibit “stress-associated hyperlocomotion” and avoidance learning deficits similar to associative learning deficits seen in human depression. Chronic administration of anti-depressants has been shown to “reliably ameliorate” these deficits (Jesberger & Richardson 1986). After 8 weeks, Buchborn and colleagues “repeatedly appl[ied]” LSD (0.13 mg/kg) subcutaneously—a dosage selected because it produces “the head-twitch response”, which has been shown to correlate with activation of 5-HT-2A receptors. Behavioural testing in a pole jumping paradigm began 5 days post-administration of the first LSD dose “to allow 5HT-2A (down-) regulation to precede the behavioural experiments”. In this paradigm, rats are placed into a chamber with an electric floor grid and must learn to avoid foot shock by jumping onto a pole. Buchborn and colleagues found that, although bulbectomized rats cannot learn to jump on the pole to avoid foot shock, LSD-treated bulbectomized rats performed as well as sham-operated rats in learning to jump on the pole to avoid the foot shock, suggesting that LSD has anti-depressant like effects in a persistent model of depression.

Although Buchborn and colleagues assume that bulbectomized rats are a good model of human depression because they exhibit similar behaviours and types of associative learning deficits, the neural mechanisms linking depressive-like behaviours and learning deficits in the rodent model are likely different, given differences in the origins of these changes in behaviour. Removing the olfactory bulbs of rodents likely impacts many more functions than those associated with mood and cognition. So, although, the rodent model offers a behavioural phenotype of an enduring form of depression compared to the behavioural phenomena produced in the FST, it is unclear what insight it offers with respect to the mechanisms by which CPs exert their therapeutic efficacy in humans with depression.

Another recent study (Hesselgrave et al. 2021) sought to assess the therapeutic impact of psychedelics in an anhedonic model of human depression. After determining the baseline hedonic state of two cohorts of 9-week-old male C57BL/6J mice using sucrose preference and female urine sniffing tests, the researchers used a 10–14-day chronic multimodal stress (CMMS) paradigm to induce anhedonia. Mice were placed daily inside an immobilizing plastic tube and exposed to strobe lighting and white noise (to block habituation (6)) for 4 hours. They were then given either a single i.p. injection of 1 ml/kg of psilocybin or saline solution (control) and placed again in the SPT and FUST 24 and 48 hours after treatment. Compared to saline injected mice, psilocybin treated mice’s preferences for sucrose solution and female urine were restored to near baseline. These findings were taken to indicate the anti-depressant effects of psilocybin. In another set of experiments in which male and female C57BL/6J treated with 1 mg/kg i.p. of psilocybin were placed in the FST, the researchers found no reduction in immobility time when assessed 1-, 3-, and 7-days post injection.

Of the rodent models of depression currently used to investigate the therapeutic effects and underlying mechanisms of CPs, it may be that the CMMS paradigm does the best job of creating a rodent model of enduring depression (compared to the FST) by impacting a rodent’s environment and experiences without extreme surgical procedures (e.g., olfactory bulbectomy). Once this rodent model is created, it can then be run through tests that assess changes in behaviour compared to baseline, using tasks that are intended to probe for depressive-like symptoms. One obvious limitation of the CMMS paradigm, however, is that it only probes for anhedonia, when MDD is associated with a list of other symptoms (See Section 2). One strategy for overcoming this limitation is to combine CMMS with a larger battery of tasks to probe for anhedonia and assess broader impacts on cognition such as those associated with human depression.

With respect to those studies that we considered in this section, it is important to note that different researchers have different intuitions about the best rodent model for studying the impact of CPs on depression and TRD, and they are at liberty to use their model of choice. Even researchers using the FST do not necessarily agree at what point to start recording a rat’s immobility, what aspects of its behaviour to document and measure, which aspects are most important for detecting depression or anti-depressant efficacy of a drug and how soon after drug delivery to assess these effects. There are other important differences across these studies with respect to—the specific CP(s) being investigated, dosage schedules, means of drug delivery, training schedules, tasks used to assess therapeutic potential, rat strains, sex and ages of rodents used. While some decisions are based on clear assumptions about model validity, others seem arbitrary. Although it is true that this research is currently in an exploratory phase, researchers working in this domain agree that the development of efficacious treatments for MDD and TRD is urgent. Thus, good reasons exist not to allow the current uncoordinated exploration, which sees investigators essentially working at cross-purposes, to carry forward, when research efforts could be better streamlined to achieve therapeutic goals.

Even if rodent researchers strive to better coordinate their practices with an eye towards reproducibility and systematic integration of empirical findings, challenges for extrapolating these findings to humans with or without depression remain. As we explained in the previous section, human clinical and neuroimaging studies have focused predominantly on how psychedelic therapy impacts human cognitive and emotional functioning and subjective phenomenological experiences. Having a “mystical experience” is thought to be key to the positive effects of CPs in neurotypical humans and essential for the therapeutic effects of CPs in humans who have autonomously elected to undergo assisted psychedelic therapy for MDD or TRD. Additionally, CPs are thought to directly impact functioning of the DMN, and clinical and neuroimaging studies (e.g., Carhart-Harris et al., 2017) indicate that TRD symptoms in humans are ameliorated via decreased activity in the DMN, and that these effects are long-lasting.

In contrast, rodent research, with few exceptions, has focused less on investigating the effects of CPs on cognitive functioning in depression compared to depressed mood. Also, CPs are directly and forcibly administered to rodents (e.g., via injection) rather than wilfully self-administered. There is also no reliable way of determining whether rats have experiences comparable to human “mystical experiences” or whether there is some correlative experience in rodents that is prerequisite for post-treatment behavioral changes like those observed in the FST.

It also seems unlikely that the underlying brain structures mediating mystical experiences and/or the psychedelic response are the same in rodents and humans, even though rodents have a structure comparable to the DMN (Gozzi & Schwarz 2016; Lu et al., 2012). In humans, DMN deactivation has been implicated in the occurrence of acute mystical experiences (Carhart-Harris et al., 2015, 2017), and findings suggest a strong correlation between the quality of mystical experiences and improved TRD symptoms (Carhart-Harris et al., 2017; Palhano-Fontes et al., 2019). Because excessive activity of the DMN has been linked with depressive symptoms including rumination and cognitive rigidity, it is thought that the subjective phenomena associated with mystical experiences lowers psychological defences and enables emotional breakthroughs in depression, disrupting excessive and repetitive patterns of negative thoughts and maladaptive cognitive schema of the “self” and “others” (Carhart-Harris et al., 2012; Mertens et al., 2020). Yet, these psychological states and changes seem to be “human specific”—it is not clear there are similar counterparts in rodents nor is it obvious how to detect them if there are. To date, researchers have used a rodent behavioral assay, “the head-twitch response”, to assess the psychedelic action of CPs in mice (see Hanks and Gonzalez-Maeso, 2013). While the HRT has predictive validity with respect to human psychedelic experiences in response to CPs, it lacks construct validity insofar as scientists cannot determine if rodents endure psychedelic experiences akin to humans in the first place.

Yet, it may be possible to bridge some of these gaps by means of cross-species translational research focused on changes in cognition rather than exclusively changes in mood. The DMN (in some form) is preserved across species (Aguilar and McNally, 2022), and using standardized behavioural assays, it may be possible to probe the psychological and phenomenological impacts of CPs in species that are closer on the phylogenetic scale to humans and intermediary between rodents and humans. There is some precedent for this approach in the neuroscientific literature on addiction. In a comparison of neuroimaging findings in humans and non-human primates (NHPs), Bradberry and colleagues have identified similarities in PFC subregions implicated in attentional bias for drug-related stimuli and lapse in self-control—distinct cognitive deficits that can be modelled in NHPs and used to inform mechanistic research in rodents (Ceceli et al., 2021).

**5.0. Positive Proposal**

The clinical, neuroimaging and rodent behavioural studies that we described in the previous two sections aim at understanding the mechanisms by which CPs bring about anti-depressant-like effects in humans. Although investigators working in both research areas confront a diverse array of epistemological challenges, to date their response to these challenges has been neither collaborative nor coordinated. Researchers working with clinical populations do not use the same recruitment criteria, study designs, treatment, dosage, and outcome measures, making it difficult to arrive at generalizable conclusions about the therapeutic effects of CPs and the implicated brain areas and underlying mechanisms that mediate them. Rodent behavioural researchers do not agree about the correct model to use to study depression in rodents, nor what drugs to test, what the dosage and treatment regimen should be and what changes rodents must exhibit to infer that a specific CP has had an anti-depressant like effect. It also is uncommon for rodent behavioural and human clinical researchers to coordinate research practices to facilitate translation of mechanistic findings from rodents to humans.

These aspects of the depression-relevant psychedelics’ research landscape are not unique to it; research aimed at identifying the mechanisms of and developing novel treatments for mental illness has historically lacked coordination. Particularly in exploratory stages of research, in the absence of understanding whether and how a drug works, methodological pluralism makes good sense; it increases the probability of novel and potentially important mechanistic discoveries. The incentive structure of science is also conducive to competition rather than collaboration across research groups investigating the same phenomenon.

Recent initiatives spearheaded by the US National Institutes of Mental Health, however, including the Cognitive Neuroscience to Improve Treatment Research in Schizophrenia (CNTRICS) initiative (e.g., Sullivan 2014, 2017) and the Research Domain Criteria (RDoC) Project (e.g., Cuthbert, 2016; Cuthbert and Insel, 2013), have stressed the importance of coordinating efforts across rodent and human studies to advance drug development particularly for the treatment of cognitive and behavioural dysfunctions that accompany mental illness. A primary aim of these initiatives has been to bring clinical researchers, cognitive neuroscientists, and rodent behavioural scientists as well as members of industry together to facilitate the translation of mechanistic findings across species.

Although these initiatives have yet to propel discovery forward, what is important for our purposes is that their very existence is suggestive of a growing recognition that therapeutic advances in mental health research require *intradisciplinary* and *interdisciplinary* collaboration, coordination of research practices across laboratories and research groups, and Open Science (OS) practices. Adopting OS strategies is the most effective way CP researchers can facilitate the dissemination of varied skills, methods, and knowledge. Given the resurgence of interest in psychedelics across the scientific community, and the recent establishment of multiple lines of inquiry into their mechanisms in neurotypical and neurodivergent brains, we anticipate that CPs will become an even larger focus of mental health research. Yet, if the current status quo is maintained, with investigators from different localities producing findings that are idiosyncratic to specific experimental contexts, study designs and methodologies, it will likely be difficult to develop a clear understanding of whether CPs hold promise with respect to treating specific mental illnesses and the mechanisms by which they work. Adopting OS practices across research groups studying the role of CPs in depression research would encourage transparency, collaboration in knowledge production, and reproducibility. Such practices would include research groups providing open access to publications, materials, methods, and data. This would allow researchers to evaluate each other’s work, gain access to the same methodologies and data, conduct similar investigations, compare findings, and in turn, assess the validity of original study results. OS also consists of sharing what considerations are behind study design and methodologies (i.e., operational definitions, rating scales, type of rodent model), along with protocols and training resources for tool use, code and software.

Collaborative multi-site studies with standardized study designs would serve to improve clinical trials at the translational front. Currently, participant pools in CP clinical studies like those described earlier in the chapter are not diverse and lack participants from under-represented groups. Given the global prevalence and burden of depression, diversity in study participation is required to represent the population to be served by therapeutic interventions. Multi-site studies would not only make study populations more representative and increase reproducibility, it would also strengthen the social infrastructure in this scientific domain by fostering collaboration and knowledge-sharing within and across research groups.

Whether multi-site clinical studies come to fruition, better harmonization of methods across research groups could serve to streamline clinical trials and neuroimaging studies and thus, accelerate mechanistic and therapeutic discoveries. For example, researchers could collaboratively agree on a set of desirable behavioural outcomes across studies. Research groups studying the same CP could standardize not only dosages and how a drug is administered, but also the type of neuroimaging techniques and cognitive/behavioural tasks used. An interesting direction might also be for studies to match points, including when to administer a second dose, conduct outcome measures, and when to use neuroimaging. Moreover, although heterogeneity and comorbidity across patient profiles is difficult to control, one way to minimize variation across studies is to prioritize similar patient characteristics, which will involve standardizing screening methods during the recruitment stage, i.e., inclusion/exclusion criteria. Lastly, two crucial features to standardize are (1) the criteria used to diagnose patients with depressions (DSM-5, depression rating scales) during the recruitment period and (2) the outcome measures used to assess changes in symptoms of depression and depression severity throughout the course of the study, along with other types of rating scales like those that measure subjective experiences. Of course, selection of criteria and measures will depend on a mutual agreement across investigators.

Ideally, these changes to structural features of research will foster better investigative practices across research groups and improve the quality of clinical research to better inform preclinical studies aimed at identifying cellular and molecular mechanisms (i.e., bedside to bench). Yet, pre-clinical research investigating the mechanisms of CPs in rodent models of depression could also benefit from multisite studies involving a collaborative network of researchers who standardize behavioral methods and engage in OS practices to facilitate mechanistic and therapeutic discovery. Ideally rodent behavioral labs would devote only some of their resources to such collaborative work, while still carrying out independent lines of hypothesis-driven and exploratory research (e.g., International Brain Lab (2017)).

Translational research would greatly benefit from closer collaboration between pre-clinical and clinical researchers. Also, given that CPs act on the serotonergic system, which is involved in learning and memory, and depression is accompanied by cognitive deficits, one viable direction for future translational work is to use standardized cognitive testing batteries to probe the impact of CPs on cognition and cognitive dysfunction across species from rodents to marmosets to humans while adopting OS practices that facilitate knowledge translation and reproducibility (see Sullivan et al., 2021).

**6.0 Conclusion**

In the last decade alone, a growing body of preliminary evidence suggests that CPs can rapidly and durably ameliorate symptoms and cognitive deficits associated with MDD and TRD. These findings have ushered many independent lines of research in rodent models of depression to determine the mechanisms by which CPs exert their therapeutic effects in humans. However, while the rise in CP research has been rapid, progress to date in understanding the brain mechanisms by which these drugs work has been slow. In this chapter, we point to current features of research practices in both clinical and pre-clinical studies to demonstrate a lack of coordination across research groups. We make the case that coordinating research practices by developing structured research communities who share knowledge, methods, and data openly, is key to accelerating future translational research.

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1. † Co-authors had equivalent input and are listed in alphabetical order.

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2. We do not review discussion of the hallucinogen 2,5-Dimethoxy-4-iodoamphetamine (DOI), a synthetic psychedelic that is somewhat similar to CPs due to its agonism of 5-HT2A. [↑](#footnote-ref-2)
3. For clinical trials on AYA in MDD see Osório et al., 2011, 2015; for a study on TRD see Palhano-Fontes et al., 2019; for a neuroimaging study on AYA in MDD see Sanches et al., 2016. [↑](#footnote-ref-3)
4. Symptoms associated with depressed mood, feelings of guilt, suicidal ideation, psychiatric anxiety, difficulties at work, and loss of libido and menstrual disturbances had the greatest reductions in scores, in comparison to baseline score. [↑](#footnote-ref-4)
5. In a separate piece of writing, this group suggests that improvements in depressive symptoms could also be corroborated by patient testimonials which are described as spiritual and mystical. See: Palhano-Fontes, F., Alchieri, J. C., Oliveira, J. P. M., Soares, B. L., Hallak, J. E., Galvao-Coelho, N., & Araujo, D. B. D. (2014). The therapeutic potentials of ayahuasca in the treatment of depression. In B.C. Labate & C. Cavnar (Eds.), The therapeutic use of ayahuasca (pp. 23-39). Springer, Berlin, Heidelberg. [↑](#footnote-ref-5)
6. Symptoms associated with apparent and expressed sadness, pessimistic thinking, suicidal ideation, and difficulty concentrating had the greatest reductions in scores, in comparison to baseline scores. [↑](#footnote-ref-6)
7. The authors note that “patients received support throughout the session from at least two investigators who remained in a room next door, offering assistance when needed” (Palhano-Fontes et al., 2019, 657). [↑](#footnote-ref-7)
8. In one of their earlier studies, participants “received detailed information on the nature of AYA, the general psychological effects of hallucinogens, and its possible adverse effects, as reported in the psychiatric literature” (Osório et al., 2015, 14), which likely impacted the generalizability of their findings. [↑](#footnote-ref-8)
9. For clinical trials on PAT in TRD see Carhart-Harris et al., 2016a, 2018; for studies involving an emotional recognition task see Mertens et al., 2020; Roseman et al., 2018b; Stroud et al., 2016; for a neuroimaging study see Carhart-Harris et al., 2017. [↑](#footnote-ref-9)
10. 12 participants were recruited in their 2016 study and 6 participants in their 2018 study; but it was reported that only 19 out of the 20 participants completed all points of depressing rating assessments. PAT was supplemented with preparatory and follow-up meetings with a clinician, psychiatrist, or therapist (i.e., some form of psychological support. [↑](#footnote-ref-10)
11. For a clinical study on PAT in MDD see Davis et al., 2020; for a 12-month follow-up study see Gukasyan et al., 2022; for a neuroimaging study on PAT in MDD involving a *set-shifting task* as a measure of cognitive flexibility see Doss et al., 2022 [↑](#footnote-ref-11)
12. GRID-HAMD is a modified version of the HAM-D. [↑](#footnote-ref-12)
13. In addition to DMT, there are early studies speculating that tetrahydroharmine mimics antidepressant properties of SSRIs. See Grob, C.S., McKenna, D.J., Callaway, J.C., Brito, G.S., Neves, E.S., Oberlaender, G., Saide, O.L., Labigalini, E., Tacla, C., Miranda, C.T., Strassman, R.J., & Boone, K.B. (1996). Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. *Journal of Nervous and Mental Disease*, *184*(2), 86–94.

    See also Callaway, J.C., McKenna, D.J., Grob, C.S., Brito, G.S., Raymon, L.P., Poland, R.E., Andrade, E.N., Andrade, E.O., & Mash, D.C. (1999). *Pharmacokinetics of hoasca alkaloids in healthy humans*. *Journal of Ethnopharmacology*, *65*, 243–256. [↑](#footnote-ref-13)
14. For studies that report on the anti-depressant effects of harmine, harmaline, and tetrahydroharmine, see Farzin et al., 2006; Fortunato et al., 2010; and Morales-Garcia et al., 2017. Pharmacological studies published by the late Dr. Jordi Riba and his research group (2001, 2003, 2006) have extensively studied the psychedelic effects of ayahuasca as a combined action between DMT and harmine. [↑](#footnote-ref-14)
15. For example, in one AYA study (Palhano-Fontes et al., 2019) participants were under “regular use” of benzodiazepines as either an anxiolytic or “supporting hypnotic.” Yet, it is not clear whether these psychoactive drugs impact participant’s experience with and response to AYA. [↑](#footnote-ref-15)
16. The HRS subscale ‘perception’ measures changes in visual, auditory, and body sensations. [↑](#footnote-ref-16)
17. Based on previous research indicating a strong relationship between these subscales which measures mystical experiences (see Studerus et al., 2016) [↑](#footnote-ref-17)
18. This objective was based on previous data in healthy participants, implicating decreased PH RSFC with LSD-evoked mystical experiences (Carhart-Harris et al., 2015). [↑](#footnote-ref-18)
19. This was one of a series of different behavioral studies to determine the impact of DMT on anxiety and depression behaviors in rodents. For reasons of space, we consider only the FST. [↑](#footnote-ref-19)