

Predicting Reactions to Psychedelic Drugs: A Systematic Review of States and Traits Related to Acute Drug Effects

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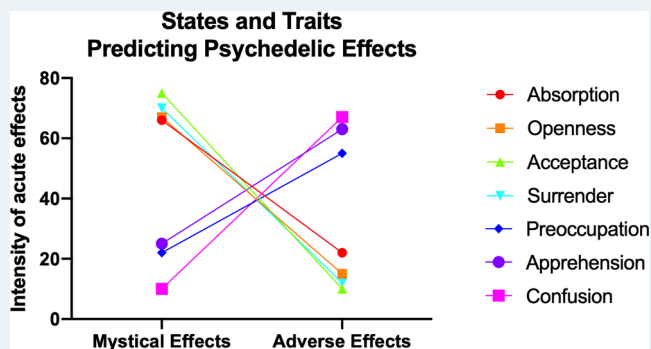
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ABSTRACT: Psychedelic drugs are increasingly being incorporated into therapeutic contexts for the purposes of promoting mental health. However, they can also induce adverse reactions in some individuals, and it is difficult to predict before treatment who is likely to experience positive or adverse acute effects. Although consideration of setting and dosage as well as excluding individuals with psychotic predispositions has thus far led to a high degree of safety, it is imperative that researchers develop a more nuanced understanding of how to predict individual reactions. To this end, the current systematic review coalesced the results of 14 studies that included baseline states or traits predictive of the acute effects of psychedelics. Individuals high in the traits of absorption, openness, and acceptance as well as a state of surrender were more likely to have positive and mystical-type experiences, whereas those low in openness and surrender or in preoccupied, apprehensive, or confused psychological states were more likely to experience acute adverse reactions. Participant sex was not a robust predictor of drug effects, but 5-HT_{2A}R binding potential, executive network node diversity, and rACC volume may be potential baseline biomarkers related to acute reactions. Finally, increased age and experience with psychedelics were individual differences related to generally less intense effects, indicating that users may become slightly less sensitive to the effects of the drugs after repeated usage. Although future well-powered, placebo-controlled trials directly comparing the relative importance of these predictors is needed, this review synthesizes the field's current understanding of how to predict acute reactions to psychedelic drugs.

KEYWORDS: *psychedelic, predictor, baseline, individual differences, screening*



"The mental effects of this material [LSD] are tremendously variable. They are completely unpredictable. You cannot tell for any given individual if he's going to have a good trip or a bad trip." – US Navy Training Film, 1967¹

Anderson Cooper: "Can you tell who is going to have a bad experience; who is going to have a transcendent experience?"

Dr. Roland Griffiths: "Our ability to predict that is almost none at all." – 60 Minutes Interview, October 13, 2019²

Psilocybin, lysergic acid diethylamide (LSD), ayahuasca/*N,N*-dimethyltryptamine (DMT), and mescaline are classic psychedelic drugs that can induce myriad cognitive,³ emotional,⁴ and neurological⁵ effects. They were investigated for their uses in treating psychiatric conditions during the mid-20th century until legal changes in the United States (US), and subsequently worldwide, halted most ongoing research.⁶ Recently, public and scientific interest into the drugs has grown as a result of promising preliminary findings published on psychedelic-assisted psychotherapy's effects on depression,⁷ substance misuse,⁸ and emotional distress associated with a variety of other chronic health conditions.^{9–11}

A pressing problem for scientific research in this area, however, is that psychedelics can also induce experiences that are markedly psychologically challenging, particularly when

used without adequate preparation and support,¹² but little is known about participant states or traits that may predict such a reaction. Identification of states and traits predicting acute psychedelic outcomes may increase the likelihood of positive therapeutic effects, reduce the prevalence of adverse reactions, and improve confidence that one is selecting a safe and effective treatment. The need for a more nuanced understanding of states and traits related to acute psychedelic reactions has become even more pressing with the recent legalization of psilocybin therapy in Oregon, which will require individuals to pass a risk assessment for goodness of fit.¹³

Although there is currently little consensus on predicting how participants will react to psychedelics based on their individual characteristics, there is some agreement regarding the influence of various factors external to the individual. Most,

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but not all,¹⁴ researchers believe that the quality or phenomenology of the acute psychedelic experience is fundamental to the drugs' therapeutic benefits.^{15–17} Therefore, the setting or context in which a psychedelic is given may be critical to predicting if individuals will experience therapeutic effects.^{18,19} Cross-culturally, psychedelic users often place emphasis on environmental factors such as ceremony, song, and ritual in the healing process.²⁰ In contemporary psychedelic trials, researchers design treatment rooms to be as comforting as possible (e.g., often set up like a living room).²¹ There are typically two guides/therapists for support, and music is played through headphones. The focus on setting is also reflected in the way many recreational psychedelic users prepare for personal sessions. When surveying individuals using 5-MeO-DMT in naturalistic settings, Lancelotta and Davis²² found that users employed environmental (e.g., preparing music), medical (e.g., obtaining a predrug medical checkup), and social (e.g., ensuring an available emergency contact) preparations in order to enhance their experience. Some indigenous cultures adopt a much different approach to the setting and healing process; for example, it may be the shaman, rather than the patient, who ingests the drug as the shaman is thought to be highly trained in interpreting and passing on spiritual and therapeutic revelations to the patient.²³

Another important external factor that may predict the effects of a psychedelic is dosage. When comparing dosages of 0, 5, 10, 20, and 30 mg/70 kg of psilocybin, Griffiths and colleagues²⁴ found dose-dependent long-term increases in life satisfaction, well-being, altruism, spirituality, positive attitudes about life and self, and positive mood changes. Importantly, ratings of fear or feeling trapped increased substantively with 30 mg/70 kg dose compared to the 20 mg/70 kg dose, suggesting somewhere in this range may be the ideal dose for optimizing treatment outcomes while minimizing adverse reactions. Dovetailing with these findings, Holze et al.²⁵ identified a ceiling effect with LSD, where positive drug effects systematically increased with dosages of 25, 50, and 100 μ g, but plateaued at the next dosage of 200 μ g, which also increased anxiety. Research has demonstrated that mystical-type experiences (i.e., marked by a sense of transcendence, joy, and awe) are more likely to be induced with higher dosages of psychedelics,^{26–28} but one study found that not all facets of mystical-type experiences are dose-dependent.²⁹ Given that mystical-type experiences have been identified as a mechanism underlying many of the benefits linked to psychedelics,^{30–32} it appears that dosage can be an important predictor of the drugs' therapeutic effects. However, much is still unknown about individual state or trait factors that may interact with known predictors like dosage.

Exclusion criteria used to screen potential participants are another useful source of information, as these criteria are ostensibly in place because researchers and/or regulators believe these variables may influence the acute experience of psychedelic drugs or increase risk for postsession complications. Individuals are generally excluded on the basis of their psychiatric or medical history (see Johnson et al.²¹ for safety guidelines). In terms of psychiatric screening, those with a personal history of schizophrenia, psychotic disorders, or bipolar disorders are excluded as there is evidence that psychedelics can trigger psychotic episodes in a subset of users,³³ those with a first- or second-degree relative with these conditions can be excluded on this basis as well.²¹ Individuals

with uncontrolled hypertension are excluded because psychedelics can acutely increase pulse as well as systolic and diastolic blood pressure.^{34,35} Pregnant women or those with inadequate birth control practices are excluded as well.²¹ Tricyclic antidepressants and lithium,³⁵ acute use of serotonin reuptake inhibitors (SSRIs),³⁷ and haloperidol³⁸ have been shown to potentiate the effects of hallucinogens, whereas chronic use of SSRIs and monoamine oxidase inhibitors have been shown to suppress their effects.³⁶ Therefore, individuals using these medications are often excluded on the basis of safety and/or experimental control.

■ THE CURRENT REVIEW

There is currently little consensus in the field on participant characteristics that can be used to predict what valence of acute effects an individual will have after taking a psychedelic drug. In modern studies, considering dosage and setting as well as excluding those with predispositions toward psychotic conditions has resulted in a high degree of safety and generally positive outcomes.³⁹ However, if the medicalization of psychedelic drugs is to continue its expansion, it is imperative that researchers and clinicians develop more specific criteria to predict the valence of acute effects for any one given individual. Moreover, improved screening methods for psychedelic treatment should reduce adverse reactions and time spent on ineffective treatments. To address this important gap in the literature, we systematically reviewed the contemporary research on baseline variables that have been shown to predict acute psychedelic drug effects. Although Studerus et al.⁴⁰ conducted an initial overview with some similar intentions, their analysis was not a systematic review, and only included studies that used psilocybin and data from their own laboratory.

■ METHODS

Search Strategy. Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).⁴¹ Two of the authors (J.S.A. and C.M.M.) independently completed the systematic search in PubMed (Figure 1). Six psychedelic-related terms (e.g., “ayahuasca”, “LSD”, “lysergic acid diethylamide”, “mescaline”, “psilocybin”, and “*n,n*-dimethyltryptamine”) were systematically cross-referenced into PubMed's search engine with seven predictor-related terms (e.g., “predict”, “correlate”, “associate”, “pre-drug”, “individual differ-

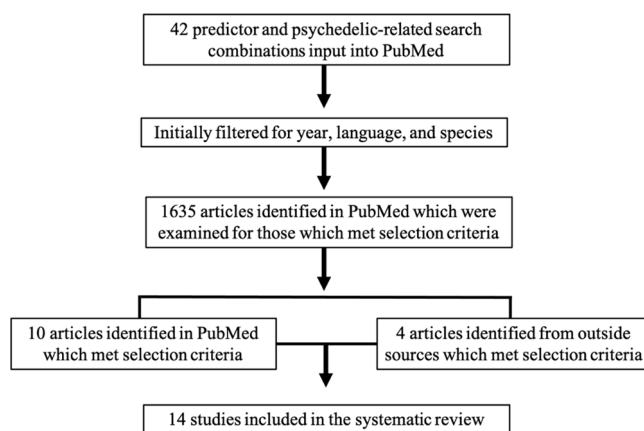


Figure 1. Flow diagram depicting the systematic search process.

ence”, “baseline”, and “risk factor”) for a sum of 42 distinct searches (e.g., “ayahuasca predict”, “ayahuasca correlate”, etc.). An initial filter was applied in PubMed to select for language (English), species (human), and year (1994–present). We chose 1994 as our cutoff for contemporary research because Strassman et al.⁴² was the first study to administer classic psychedelic compounds to human participants in the US after several decades of prohibition.

Selection Criteria. After filtering for language, species, and year, articles were examined for those which met the following criteria: (1) They were published in a peer-reviewed journal. (2) Classic psychedelic drugs were used. (3) Predrug measures were predictive of an acute effect. Book chapters, case reports, and reviews were excluded. Discrepancies regarding study inclusion were resolved by evaluating the study together with multiple members of the research team.

RESULTS

Study Selection. The 42 PubMed searches generated a total of 1635 articles, which were assessed by the two searchers for those that fulfilled the selection criteria. This led to the identification of 10 articles that met the criteria for our review, and 4 others were identified by the authors from outside sources (e.g., referenced in other articles, published after our systematic search, etc.), for a total of 14 articles included in the systematic review (Table 1).

The review included 10 articles using psilocybin,^{12,40,43–50} 2 using LSD,^{51,52} 1 using ayahuasca,⁵³ and 1 examining psychedelic use in general.⁵⁴ Sample sizes ranged from 10–1993 ($M = 108.75$, $SD = 91.95$), and 6 out of 14 articles included control conditions. The median year of publication was 2018, suggesting that this is an emerging area of research. Baseline predictors of psychedelic drug effects could be broadly broken down into two categories: states and traits (Table 2; see also Supplementary Table 1 to see data organized by outcomes rather than by baseline predictors).

Drugs. Psilocybin. We will begin by reviewing the studies that identified biological measures that were predictive of the effects of psilocybin. Although they will need further verification, these variables could potentially be used as biomarkers for screening participants in future research or clinical settings. One study found that predrug individual differences in 5-HT_{2A}R binding potential predicted how individuals responded to psilocybin.⁵⁰ Lower baseline 5-HT_{2A}R binding was associated with longer peak effects, a more rapid decrease in subjective drug intensity (SDI), and higher ratings of mystical-type experience. The authors suggested that greater predrug serotonin receptor availability could lead to more effective receptor stimulation and more intense effects. Longer peak effects could allow mystical-type experiences to intensify, and a rapid return to baseline consciousness may make the effects more salient. Therefore, predrug 5-HT_{2A}R binding may be an important biomarker for predicting the effects of psychedelics. The small sample size ($N = 16$) and lack of control group in this study are important limitations, however.

In a placebo-controlled trial, Lebedev et al.⁴⁴ found that individuals with a lower diversity of executive network nodes at baseline (i.e., those with more efficient network segregation) were more likely to experience ego dissolution under the influence of psilocybin. The authors interpreted these results to be in line with the notion that efficient network segregation is related to firm ego boundaries and that individuals with

typically firm boundaries are more sensitive to the ego-dissolving effects of psilocybin. However, the study was limited by a small and homogeneous sample ($N = 15$; female = 2). Nonetheless, given that ego dissolution has been identified as a mechanism underlying some of the positive long-term benefits of psychedelics,^{55–57} executive network node diversity may be an important predictor to evaluate further.

Another placebo-controlled study found that structural neural measures could be used to predict aspects of the psychedelic experience.⁴⁵ Here, baseline right hemisphere rostral anterior cingulate (rACC) thickness positively predicted feelings of spiritual experience and insightfulness while healthy volunteers were under the influence of psilocybin. Given the rACC's high concentration of 5-HT_{2A} receptors and role in emotional processing,⁵⁸ the authors hypothesized that activity in the cingulate cortex may underlie the profound emotional experiences induced by psychedelics. Although the study was limited by using varied dosages within the treatment condition (e.g., 0.16 mg/kg or 0.215 mg/kg), it was strengthened by the use of a relatively large and heterogeneous sample ($N = 55$; female = 22).

Bienemann et al.⁴³ performed a quantitative text analysis of negative psilocybin reports posted to the website Erowid. They found that “bad trips” were more frequently reported by female users, suggesting that sex may be a predrug variable related to how individuals respond in a recreational setting. However, the effect size was small ($V = 0.20$), and this study was hampered by a number of methodological limitations, including self-selection and recall biases, varied dosages, varied settings, unknown drug purities, and a large amount of missing data.

Contradicting these results, Russ et al.⁴⁶ found few sex differences other than that for females apprehension was significantly more negatively correlated with mystical-type experiences compared to that in males. This study also identified that predrug states of preoccupation and confusion were positively related to adverse reactions, whereas the trait of openness was negatively correlated with adverse outcomes. Ego dissolution and mystical-type experiences were positively related to baseline measures of surrender (i.e., willful release of one's goals, constructs, habits, and preferences), absorption (i.e., individual's openness to diverse cognitive, perceptual, and imaginative experiences as well as value of aesthetics and nature), and spiritual motivations, as well as negatively correlated with measures of deservingness and apprehension. Although the study had a large and heterogeneous sample ($N = 183$; female = 85), it was limited by a retrospective design and varied dosages.

In another study, Russ and colleagues⁴⁷ once again identified that baseline measures of surrender ($r = 0.72$) and absorption ($r = 0.61$) moderately to strongly predicted the extent to which one had a mystical-type experience. Here, surrender was also positively related to spiritual change and long-term positive change, as well as negatively associated with acute experiences of dread and long-term negative change. Measures of absorption were also positively correlated with spiritual change and long-term positive change and negatively related to dread. Experiences of dread were positively related to baseline measures of preoccupation ($r = 0.64$) and confusion ($r = 0.58$) and were negatively correlated with age ($r = -0.23$). Finally, baseline measures of age and barriers (i.e., tendency to reject phenomena that have no rational explanation) were negatively related to acute mystical-type experiences. This study had similar strengths and weaknesses as Russ et al.;⁴⁴ the

Table 1. Articles That Met Selection Criteria

authors	year	population/ diagnosis	drug	dosage (ROA)	sample size	control condition	baseline predictor variable	state (S) or trait (T)	outcome predicted	direction of relationship (±)
Bienemann et al. ^{4,43}	2020	unselected	psilocybin	varied	346	no	gender (female)	T	"bad trip"	+
Bouso et al. ⁵³	2013	users	ayahuasca	100 mL (oral)	24	yes	lifetime ayahuasca use	T	acute impairment in executive function	-
Carbonaro et al. ^{4,12}	2016	unselected	psilocybin	varied	1993	no	age history of psychedelic use	S	difficulty of experience	-
Carhart-Harris et al. ³¹	2015	healthy	LSD	40–80µg (IV)	10	yes	conscientiousness mental imagery ability history of psychedelic use	T	difficulty of experience	-
							openness absorption	T	acute changes in suggestibility acute changes in mental imagery	+
							clear intention	T	wellbeing	-
Haijen et al. ⁵⁴	2018	unselected	varied	varied	212–654	no	set recreational intention executive network node diversity	T	mystical experience challenging experience visual effects	+
							right rACC volume	S	mystical experience visual effects	+
Lebedev et al. ⁴⁴	2015	healthy	psilocybin	2 mg (IV)	15	yes	surrender	S	challenging experience	+
Lewis et al. ⁴⁵	2020	healthy	psilocybin	0.16 or 0.215 mg/kg (oral)	55	no	absorption spiritual motivations	S	challenging experience	+
							deservingness	S	ego dissolution	-
							apprehension	S	intensity of acute emotional experience	-
Russ et al. ^{4,46}	2019	unselected	psilocybin	varied	183	no	gender (female) preoccupation confusion openness surrender	T	mystical experience ego dissolution ego dissolution mystical experience ego dissolution apprehension/mystical experience relationship	+
							absorption	T	mystical experience ego dissolution	+
							adverse experience	S	ego dissolution	-
							adverse experience	S	mystical experience	-
							adverse experience	S	ego dissolution	-
							adverse experience	S	adverse experience	+
							adverse experience	T	adverse experience	+
							adverse experience	S	mystical experience dread	+
Russ et al. ^{4,47}	2019	unselected	psilocybin	varied	143	no	absorption	T	mystical experience	+

Table 1. continued

authors	year	population/ diagnosis	drug	dosage (ROA)	sample size	control condition	baseline predictor variable	state (S) or trait (T)	outcome predicted	direction of relationship (±)
Smigielski et al. ⁴⁸	2019	expert Buddhist meditators	psilocybin	315 µg/kg (oral)	39	yes	barriers	S	dread	-
							age	S	mystical experience	-
							preoccupation	S	mystical experience	-
							confusion	S	dread	-
							optimistic attitude toward life	T	dread	+
Stauffer et al. ⁴⁹	2020	long-term AIDS survivors	psilocybin	0.3–0.36 mg/kg	18	no	openness	T	visionary restructuring	+
							reappraisal of emotions	T	oceanic boundlessness	+
							acceptance	T	mystical experience	+
							meditation depth	T	oceanic boundlessness	+
							attachment anxiety	T	mystical experience	+
Stenbaek et al. ⁵⁰	2020	healthy	psilocybin	0.2–0.3 mg/kg (oral)	16	no	Attachment avoidance	T	challenging experience	+
							5-HT _{2A} R binding potential	T	peak plateau latency	-
							age	S	subjective drug intensity comedown latency	+
							history of psychedelic use	T	mystical experience	-
							acute impaired control and cognition	S	acute impaired control and cognition	-
Studerus et al. ⁴⁰	2012	healthy	psilocybin	115–315 mg/kg (oral)	261	yes	acute disembodiment	T	acute disembodiment	-
							visionary restructuring	T	visionary restructuring	-
							acute changed meaning of percepts	T	acute changed meaning of percepts	-
							acute blissful state	T	acute blissful state	+
							acute audio–visual synesthesia	T	acute audio–visual synesthesia	+
							complex imagery	S	complex imagery	+
							spiritual experience	S	spiritual experience	+
							acute anxiety	S	acute anxiety	+
							acute general consciousness alteration	S	acute general consciousness alteration	+
							insightfulness	S	insightfulness	+
acute audio–visual synesthesia	S	acute audio–visual synesthesia	+							
acute oceanic boundlessness	S	acute oceanic boundlessness	-							
acute blissful state	T	acute blissful state	-							
complex imagery	T	complex imagery	-							
acute oceanic boundlessness	T	acute oceanic boundlessness	+							
visionary restructuring	T	visionary restructuring	+							
spiritual experience	T	spiritual experience	-							

Table 1. continued

authors	year	population/ diagnosis	drug	dosage (ROA)	sample size	control condition	baseline predictor variable	state (S) or trait (T)	outcome predicted	direction of relationship (\pm)
Terhune et al. ⁵²	2016	healthy	LSD	40–80ug (IV)	10	yes	absorption	T	acute audio–visual synesthesia stimulus-color consistency	+ –

^aRetrospective study design.

sample was large and sex-diverse ($N = 143$; female = 62) but used a retrospective design and therefore could not control dosage, setting, or drug purity.

When evaluating the use of psilocybin in combination with a mindfulness retreat in a sample of expert Buddhist meditators, Smigielski et al.⁴⁸ identified several traits that were predictive of drug effects. Mystical-type experiences were positively related to baseline measures of optimistic attitudes toward life, openness, acceptance, and meditation depth. Optimistic attitudes toward life were also predictive of acute experiences of visionary re-structuralization (i.e., changes in elementary and complex imagery) and oceanic boundlessness (i.e., mystical-type experiences). Pre-drug measures of openness and meditation depth were also positively related to oceanic boundlessness. Although some participants had previous experience with psychedelics and others did not, in general, this study was methodologically strong as it was placebo-controlled and double-blind, had a respectable sample size ($N = 38$; female = 15), and included a long-term follow-up (e.g., 4 months).

Using a pooled analysis of 23 studies from the same laboratory involving 409 psilocybin sessions with 261 healthy volunteers, Studerus et al.⁴⁰ identified a number of states and traits that were predictive of acute effects. First, absorption was positively related to most facets of oceanic boundlessness (e.g., experience of unity, spiritual experience, insightfulness, and disembodiment) and all facets of visionary re-structuralization (e.g., complex imagery, elementary imagery, audio–visual synesthesia, and changed meaning of percepts). Individuals high in the trait of sociability were less likely to have a spiritual experience and more likely to experience audio–visual synesthesia. Histories of cannabis and alcohol consumption were related to increases in blissful states and audio–visual synesthesia, respectively. In terms of state predictors, they found that age was negatively related to acute impairments in control and cognition. Emotional excitability predicted acute increases in spiritual experience, insightfulness, audio–visual synesthesia, general consciousness alteration, and anxiety. Last, baseline state-level measures of general psychological distress were negatively correlated with oceanic boundlessness, blissful states, and complex imagery. Although dosages varied across some of the experiments, this analysis was methodologically rigorous given its large sample size ($N = 261$; female = 100), and all studies were placebo-controlled.

Stauffer and colleagues⁴⁹ administered 0.3–0.36 mg/kg of psilocybin to long-term AIDS survivors experiencing demoralization. They found that those high in the trait of attachment anxiety at baseline were more likely to have mystical-type experiences ($r = 0.53$), and those high in attachment avoidance were more likely to have challenging experiences ($r = 0.62$). The authors hypothesized that hyperactivating strategies (i.e., cognitive and behavioral efforts to reduce distance from intimate others) commonly used by those with high attachment anxiety may prime individuals for interconnectedness, a defining feature of mystical-type experiences. The correlation between attachment avoidance and challenging experiences was thought to reflect the aversion to emotional vulnerability and difficulty with novel experiences characteristic of those high in attachment avoidance. However, this study was limited because of its open-label design, small sample size ($N = 18$), and homogeneous sample (i.e., almost exclusively older men with history of psychedelic use).

Table 2. Summary of Relevant States and Traits

	baseline predictor	outcome(s) and direction of relationship (\pm)	refs
	age	mystical experience (–), dread (–), acute impaired control and cognition (–), adverse experience (–)	12, 40, 47
	apprehension	mystical experience (–), ego dissolution (–), adverse experience (+)	46, 47
	barriers	mystical experience (–)	47
	clear intention	mystical experience (+), visual effects (+)	54
	confusion	dread (+)	46, 47
	deservingness	mystical experience (–), ego dissolution (–)	46
	emotional excitability	spiritual experience (+), acute anxiety (+), general consciousness alteration (+), insightfulness (+)	40
states	general psychological distress	oceanic boundlessness (–), blissful state (–), complex imagery (–)	40
	preoccupation	dread (+)	47
	recreational intention	challenging experience (–)	54
	set	challenging experience (–)	54
	spiritual motivations	mystical experience (+), ego dissolution (+), apprehension/mystical experience relationship (+)	46
	surrender	mystical experience (+), ego dissolution (+), spiritual change (+), dread (–)	46, 47
	5-HT _{2A} R binding	peak plateau latency (–), subjective drug intensity comedown latency (+), mystical experience (–)	50
	absorption	mystical experience (+), challenging experience (+), visual effects (+), ego dissolution (+), dread (–), spiritual change (+), acute oceanic boundlessness (+), acute visionary restructuralization (+), stimulus-color consistency (–)	40, 46, 47, 52, 54
	acceptance	mystical experience (+)	48
	alcohol consumption	audio–visual synesthesia (+), visual effects (+)	40
	attachment anxiety	mystical experience (+)	49
	attachment avoidance	challenging experience (+)	49
	cannabis consumption	blissful state (+)	40
	conscientiousness	suggestibility (+)	51
traits	executive network node diversity	ego dissolution (+)	44
	gender (female)	“bad trip” (+), apprehension/mystical experience relationship (+)	43, 46
	history of psychedelic use	acute impairment in executive functioning (–), adverse experience (–), wellbeing (–), acute disembodiment (–), visionary restructuralization (–)	12, 40, 53, 54
	meditation depth	mystical experience (+), oceanic boundlessness (+)	48
	mental imagery ability	acute changes in mental imagery (+)	51
	openness	adverse experience (–), oceanic boundlessness (+), mystical experience (+)	54, 46, 48
	optimistic attitude toward life	visionary restructuralization (+), oceanic boundlessness (+), mystical experience (+)	48
	reappraisal of emotions	anxious ego dissolution (–)	48
	right rACC volume	intensity of acute emotional experience (+)	45
	sociability	spiritual experience (–), acute audio–visual synesthesia (+)	40

Finally, Carbonaro et al.¹² surveyed psilocybin users about their most challenging experience with the drug. Weak, but statistically significant, relationships were found between age ($r = -0.06$) and history of hallucinogen use ($r = -0.05$) with difficulty of the experience. Although the study had a large sample size ($N = 1993$), its retrospective design, homogeneous sample (78% male, 89% White, and 87% had at least some college education), and variable dosages as well as settings are important limitations to keep in mind.

LSD. Two articles were included that identified baseline measures predicting the acute effects of LSD, but it seems both studies relied on the same sample of participants. The researchers first found that baseline measures of conscientiousness were strongly correlated with acute changes in suggestibility ($r = 0.89$).⁵¹ Given that suggestibility has been argued to be one factor underlying the drugs' transdiagnostic benefits,³⁹ baseline measures of conscientiousness could be an

important predictor to include when screening participants. The authors also found that predrug mental imagery ability was positively correlated with acute increases in vividness of mental imagery ($r = 0.72$).

In another analysis of the same sample of participants as Carhart-Harris et al.,⁵¹ researchers found that absorption was negatively related to stimulus-color consistency during synesthesia-like experiences with LSD ($r = -0.67$).⁵² The authors concluded that synesthesia-like experiences are not more consistent under LSD than placebo and that proneness to states of absorption may moderate this relationship. Although these two studies were placebo-controlled, they were limited by a small and nondiverse sample ($N = 10$; female = 1), variable dosages (e.g., 40–80 μg), and participants had considerable past experience with the drug (M number of LSD experiences = 65).

Ayahuasca. Only one study identified a predictor of the effects of ayahuasca in our search. Bouso et al.⁵³ found that while under the influence of ayahuasca, experienced users (i.e., >60 uses) had less impairment than occasional users (i.e., 8–60 uses) on a test of executive functioning. Additionally, across both groups, impaired performance in executive functioning was inversely correlated with lifetime ayahuasca use ($r = -0.62$). This indicates that previous experience with psychedelics may confer compensatory or neuromodulatory effects that buffer against acute cognitive impairments. Although the sample size was modest ($N = 24$; female = 12), the study was sex-balanced and included a control group consisting of drug-naïve participants to rule out learning effects.

Psychedelics Not Otherwise Specified. Given that classic psychedelics generally share more similarities than differences in their effects,⁵⁹ some studies have examined predictors related to psychedelic use in general. In a prospective study, researchers surveyed users 1 week prior, 1 day before, 1 day after, 2 weeks after, and 4 weeks following the day they planned to use a psychedelic.⁵⁴ The trait of absorption was once again an important predictor of effects as it was positively related to mystical-type experiences, visual effects, as well as challenging experiences. Having a clear intention and positive “set” (i.e., one’s state of mind immediately prior to drug intake) were conducive to mystical-type experiences and visual effects and decreased the likelihood of a challenging experience. A recreational intention was also negatively related to challenging experiences. Although the study was strengthened by a large sample size ($N = 212-654$) and multiple follow-ups, it was limited by attrition as well as varied substances, dosages, and settings.

DISCUSSION

Individual responses to psychedelic drugs are notoriously difficult to predict; however, this review indicates that there may be baseline traits and states that are important to consider. Given that the median year of publication for the included articles was 2018, it seems researchers are just beginning to understand how to predict psychedelic drug effects. Next, we will coalesce this burgeoning research.

Traits. In terms of biological predictors, 5-HT_{2A}R binding potential,⁵⁰ executive network node diversity,⁴⁴ and rACC volume⁵⁴ were shown to be related to the acute cognitive and emotional effects of psychedelic drugs. Given the high cost of collecting neuroimaging measures, it may be some time before these indices can be practically implemented into clinical screening procedures. Nevertheless, there is clear utility in researchers continuing to delineate biomarkers predictive of drug effects, as they can reduce participant and experimenter biases.⁶⁰ One biological measure that was collected in every study was participant sex; however, only a single study found that adverse reactions with psilocybin were more likely to be reported by female users.⁴³ Other studies that included measures of adverse reactions did not identify sex differences,^{12,48,54} and there are alternative explanations to the findings of Bienemann et al.⁴³ For example, given their self-report design, the results could be explained by the tendency for women to be more likely to disclose negative emotional experiences than men.⁶¹ Moreover, research has demonstrated that there are no sex differences in 5-HT_{2A}R distribution⁶² nor in the pharmacokinetic profiles of psychedelics.^{63–65} In short,

it seems that psychedelic drugs induce generally similar effects in males and females.

Absorption was the personality trait most consistently linked to psychedelic drug reactions, as it was related to higher ratings of mystical-type experience⁵⁴ and ego dissolution.⁴⁶ Individuals high in absorption were also particularly susceptible to the perceptual effects of the drugs, as absorption predicted heightened visual effects⁵⁴ and visionary restructuralization⁴⁰ as well as decreased stimulus–color consistency during synesthetic-like experiences.⁵² These findings are in line with previous research noting that absorption is a predisposing trait for hallucinatory experiences across a variety of altered states.⁶⁶ Critically, across several studies and research groups, absorption was a replicable predictor of mystical-type experiences.^{40,46,47,54} Given the role of mystical-type experiences in facilitating therapeutic changes with psychedelics,³⁹ it appears the trait of absorption may be an important variable to consider when evaluating if psychedelics are likely to be an effective treatment for an individual. Moreover, absorption has been shown to be related to 5-HT_{2A}R binding potential,⁶⁷ which is consistent with recent research indicating that 5-HT_{2A}R binding potential may be a biomarker for predicting psychedelic drug effects.⁵⁰

Openness to experience, a personality trait highly correlated with absorption,⁶⁸ was also related to positive effects, such as mystical-type experiences⁴⁸ and fewer adverse reactions.⁴⁶ Additionally, acceptance was related to mystical-type experiences.⁴⁸ Thus, absorption, openness, and acceptance may represent a set of related personality traits that prime individuals to fully immerse themselves in, and be more accepting of, a nonordinary state.

In addition to personality traits, one’s personal history of psychedelic use was shown to predict how individuals responded on several measures. In general, drug effects were less intense in those with greater psychedelic usage in the past, suggesting that users may habituate or become desensitized to the effects of psychedelics over time. Indeed, history of psychedelic use was negatively related to disembodiment,⁴⁰ visionary restructuralization,⁴⁰ and acute impairment in executive functioning.⁵³ These changes did not seem to be valence-specific, as greater previous use was related to reduced difficulty of the experience¹² as well as reduced improvements in well-being post-treatment.⁵⁴ One interpretation of these results is that users may habituate to the effects of psychedelics after repeated usage, and it may be important to not overuse psychedelic substances in order to continue deriving the same benefits from them. Many users report psychedelic states as being drastically different than typical waking consciousness; this novelty may be one factor contributing to “pivotal mental states” that underlie rapid psychological transformation with the drugs.⁶⁹ Although it is not unusual in some cultures to continue taking psychedelics on a regular basis (e.g., ayahuasca as much as 4 times per week),⁷⁰ it is unclear if these users continue to experience the same intensity of acute effects or long-term benefits from any given session.

States. An individual’s expectations and mood immediately prior to drug intake, commonly referred to as one’s “set”, have been long argued to be critical variables in determining acute psychedelic effects.^{71–73} Those who approach the session with an open and positive mindset are thought to be more likely to derive benefits, whereas those in an unstable state or negative mindset are more likely to experience adverse effects.^{74,75} This notion was validated by our findings, as having a positive set

decreased the likelihood of having a challenging experience.⁵⁴ Similarly, states of apprehension, confusion, and distress predicted more adverse reactions and less likelihood for a mystical-type experience.^{40,46,47} A state of surrender, in particular, emerged from our synthesis of the literature as an important predictor of drug effects. Those high in surrender were more likely to experience ego dissolution as well as mystical-type experiences and were less likely to experience acute dread.^{46,47} A state of surrender may contribute to the positive effects of psychedelics in a similar way as the traits of absorption, openness, and acceptance, that is, by making individuals more susceptible to immersing themselves in the experience and “letting go” of previous self-narratives or attitudes.⁷⁶

In addition to expectations and mood, the motivations and intentions for a psychedelic experience were predictive of how individuals responded. Spiritual motivations were related to increased likelihood of mystical-type experiences and ego dissolution.⁴⁶ Clear intentions were also predictive of mystical-type experiences, and those with a recreational intention were less likely to report challenging experiences.⁵⁴ Therefore, in addition to traits, expectations, and mood, researchers and clinicians should consider patients' intentions when predicting how an individual will respond to a psychedelic drug.

The age at which participants consumed a psychedelic substance was related to several outcomes. As age increased, participants tended to experience slightly less intense effects, both positive and negative. Age was negatively related to difficulty of the experience,¹² experiences of dread,⁴⁷ mystical-type experiences,⁴⁷ and acute impaired control and cognition.⁴⁰ Thus, older individuals may be somewhat less sensitive to the effects of psychedelics drugs and/or potentially require higher doses. This is in line with other research indicating that there may be concomitant changes with age that can interact with drug potencies (e.g., increased body weight, higher number of other medications, and decreases in 5-HT_{2A}R binding potential).^{72,77}

Limitations. There are a number of important limitations to keep in mind when interpreting findings from this review. First, our methodological critique of the literature revealed that many studies were compromised by open-label designs, small sample sizes, and/or homogeneous samples. Additionally, retrospective designs using online crowd-sourcing methods may have been compromised by self-selection biases. However, these are not problems inherent to psychedelic science per se as they could be rectified with increased funding for larger, placebo-controlled trials with diverse samples. Another limitation is that many of the relationships identified in this review have yet to be replicated. However, given that many of the studies identifying baseline predictors of drug effects were recently published, it may be that researchers have not been fully aware of the findings or have not yet had sufficient time to pursue replication work; our review can address the first issue by bringing these variables to researchers' attention and inspiring further study in this area. Last, it is worth noting that researchers often fail to report when there is an absence of a relationship between variables.⁷⁸ This “file drawer” problem may have produced unpublished results that run contradictory to our findings, resulting in potential Type I errors. Nonetheless, this review can provide guidance for future researchers aiming to identify potential replicable predictors.

Future Directions. In addition to addressing the aforementioned limitations, there are myriad future directions

researchers can explore to improve our understanding of how to predict acute effects of psychedelic drugs. First, now that a set of baseline variables related to drug effects has been identified, future researchers should compare the relative importance of these predictors by including them within the same studies and statistical models. Doing so can ultimately inform an optimal and concise set of screening procedures for individuals planning to take a psychedelic. We particularly endorse future researchers evaluating the trait of absorption and state of surrender (which are moderately correlated with one another),⁴⁷ as they were consistently related to positive experiences with psychedelics and the strength of these relationships were often moderate-to-strong. Across cultures and spiritual orientations, those high in absorption are more likely to have spiritual experiences;⁷² our results suggest that this effect generalizes to mystical-type experiences under psychedelics, which are often described as spiritually significant.

If states and traits that facilitate the benefits of psychedelics become firmly established, then a natural question will be how to alter those baseline variables to enhance treatment effects. For example, if absorption is an important individual difference related to positive responses to psychedelics, then increasing absorption pretreatment may make the therapy more effective. Speculatively, given that microdosing psychedelics (i.e., regularly taking a non-hallucinogenic dose) has been shown to increase absorption,⁷⁹ it is conceivable that incorporating microdosing before a full treatment dose could be beneficial. However, state-level factors would ostensibly be easier to alter than traits, which are more stable. That is, participants' mood, expectations, and intentions can be primed during predrug preparatory counseling to optimize treatment outcomes.

■ CONCLUSION

For decades, identification of baseline variables that predict the effects of psychedelic drugs has proven illusory. Although the findings presented here are not definitive, they can serve as an important synthesis of the evidence scientists have compiled to date. This information will become increasingly valuable as psychedelic substances continue to be decriminalized and incorporated into medical contexts.⁷² Those high in the traits of absorption, openness, and acceptance as well as a state of surrender may represent ideal candidates for psychedelic therapy. In contrast, individuals low in those traits or that are in preoccupied, apprehensive, or confused states are more likely to experience adverse reactions. Although participant sex was not a robust predictor, 5-HT_{2A}R binding potential, executive network node diversity, and rACC volume were baseline biological measures related to acute reactions. Increased age and experience with psychedelics were individual differences related to generally less intense effects with the drugs. Future studies should address current experimental limitations by using well-powered, placebo-controlled designs with more diverse samples. Nonetheless, this review serves as an important synthesis of how to predict reactions to psychedelic drugs. Application of this knowledge could have broad implications for psychedelic science, including increasing confidence in treatment selection, saving resources spent on ineffective treatments, attenuating the prevalence of adverse reactions, and improving therapeutic efficacy.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acspsci.1c00014>.

Table with the results of our review organized by outcome measure rather than by predictors (XLSX)

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