

## **Treatment Expectation is the Strongest Predictor of Willingness to Participate in Psychedelic Clinical Trials**

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**ABSTRACT**

**Background and Aims:** Understanding the factors that lead to participation in psychedelic clinical trials is essential for assessing potential biases in enrollment and ensuring the generalizability of findings. Psychedelic treatment is thought to impact personality traits, psychological flexibility, and expectations, however these non-pharmacological variables may also influence the initial decision to participate. This study aimed to identify factors associated with the willingness to participate in a psychedelic trial.

**Methods:** A cohort of chronic pain patients (N = 988) completed a survey assessing their interest in participating in a psychedelic clinical trial and the Big Five personality traits. A subset (N = 235) were re-surveyed for additional data on psychological flexibility and outcome expectations. Logistic regression analyses were conducted to measure the associations between these factors and participants' willingness to participate.

**Results:** Trait openness to experience, and positive outcome expectations, were associated with a greater likelihood of willingness to participate, while negative outcome expectations predicted lower willingness. When controlling for all variables, negative expectancy emerged as the strongest and only significant predictor.

**Conclusions:** The results show that negative outcome expectations play a role in who chooses to participate in psychedelic clinical trials, suggesting that current trials are biased toward including participants who are more risk tolerant. As psychedelic therapies enter mainstream medical practice, broader populations undergoing psychedelic treatment may not see the same therapeutic outcomes observed in current trials. These findings highlight the need to account for expectancy effects in study enrollment to prevent overestimation of efficacy and improve generalizability.

*Keywords:* psychedelics, willingness to participate, expectations, personality, openness

## INTRODUCTION

Interest in psychedelic therapies has surged in recent years, with clinical trials reporting promising therapeutic effects for conditions such as depression, post-traumatic stress disorder (PTSD), anxiety, and substance use disorders (De Gregorio et al., 2021; Holze et al., 2024; Kugel et al., 2025; Yao et al., 2024). As these treatments move toward broader clinical application, it is critical to examine the factors that influence participation in psychedelic trials and their associated therapeutic outcomes. One key issue in psychedelic research is self-selection bias, wherein individuals predisposed to favorable outcomes may be more likely to enroll in clinical trials. Failing to account for this bias may lead to inflated efficacy estimates and limit generalizability of results to broader populations.

Non-pharmacological factors, such as “set”—which includes an individual’s personality traits, mental states, cognitive processes, and expectations—play a complex role in psychedelic trials (Pronovost-Morgan et al., 2023). Psychedelic treatment may change personality traits, psychological flexibility, and expectations. In particular, psychedelic use is associated with increased trait openness and decreased neuroticism (e.g. Bouso et al., 2018; Erritzoe et al., 2018; Pagni et al., 2025; Weiss et al., 2021), increased psychological flexibility (Close et al., 2020; Davis et al., 2020; Pilecki et al., 2024; Sloshower et al., 2024), and altered expectations about the world around them (Colloca et al., 2023).

These same factors may independently influence therapeutic outcomes in psychedelic trials. Individuals high in trait openness are more likely to have positive and mystical-type experiences, whereas those low in openness are more likely to experience acute adverse reactions (Aday et al., 2021). Previous research has found that psychological flexibility, the ability to be aware of and open to experiences and act in alignment with one’s values (Hayes et al., 2006), impacts

psychedelic treatment outcomes (Agin-Liebes et al., 2022; Close et al., 2020). Expectancy plays a critical role in psychedelic clinical trials, particularly given the challenges of maintaining effective blinding in these studies, but is rarely assessed in psychedelic trials (Szigeti & Heifets, 2024).

Finally, these factors may predispose certain individuals to seek enrollment in these studies.

Individuals high in openness may be more likely to seek out and benefit from psychedelic experiences, creating a positive feedback loop in which increased openness acts as both a precursor and a consequence of psychedelic use (Sjöström et al., 2024; Weiss et al., 2023).

Similarly, individuals with greater psychological flexibility are more likely to engage in challenging experiences in pursuit of a meaningful life (Kashdan, 2010), and tend to be more extraverted, sensation-seeking, open to experience, and agreeable (Čekrljija & Schermer, 2024; Chen et al., 2022). These tendencies could translate to a greater willingness to participate in psychedelic trials, as individuals high in psychological flexibility are more open to seeking mental health care and more indifferent to stigma (Fogle et al., 2022; Komiya et al., 2000).

Lastly, it is possible that the recent widespread exuberant media coverage on psychedelics has created positive treatment expectations which encourage individuals to seek out psychedelic trial participation (Aday et al., 2022). While experts have called for investigation into these potential sources of bias, it remains very poorly documented (Sjöström et al., 2024; Szigeti & Heifets, 2024). Understanding these determinants will not only clarify who is most likely to engage in psychedelic therapies but will also provide insights into who is most likely to respond favorably to them.

Here, we aimed to identify the factors associated with willingness to participate in psychedelic trials. Specifically, we examined the extent to which: (1) personality traits are associated with

willingness to participate, and (2) psychological flexibility and outcome expectations are associated with willingness to participate. Using a cohort of chronic back pain patients, we assessed these relationships in the context of an actual psychedelic trial, offering a unique opportunity to evaluate self-selection bias. As such, this study provides insight into how pre-existing participant characteristics may bias psychedelic trial enrollment and, in turn, impact generalizability of findings.

## **METHODS**

### **Participants and Procedure**

All procedures were reviewed and approved by the Stanford University Institutional Review Board (IRB #64474) and in accordance with the Declaration of Helsinki. All participants provided electronic informed consent, which outlined the study's purpose, procedures, rights, and potential risks and benefits. Consent was obtained by participants acknowledging their understanding and agreement before proceeding with the survey.

Data collection took place between November 2022 and August 2023 and involved administering questionnaires to a registry of 6808 chronic pain patients who had previously consented to be contacted by Stanford University for future research opportunities. Data collection occurred in two stages (Callahan et al., 2023). During the first round of data collection, participants completed a questionnaire measuring the Big Five personality traits, introduced as follows: "You are invited to take part in a research study that will help us examine the personality traits related to interest in a new treatment for chronic pain". During the second round of data collection, the same participants were invited to complete additional questionnaires assessing psychological flexibility, outcome expectancies, mental and physical health, duration of pain, as well as

demographic information (age, gender, race, ethnicity, relationship status, employment status). A total of 988 participants completed the first round of data collection, and of those, 235 completed the second round.

## **Measures**

### *A Brief Version of the Big Five Personality Inventory-10 (BFI-10)*

The BFI-10 (Rammstedt & John, 2007) is a validated, brief measure of the Big Five personality traits: openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism. This inventory consists of 10 items, with two items per trait (one of which is reverse-scored), to efficiently capture key dimensions of personality. Participants rated each item on a 5-point Likert scale ranging from 1 (“Disagree strongly”) to 5 (“Agree strongly”). After reverse-scoring where necessary, the two items corresponding to each trait are aggregated, with higher scores indicating higher levels of that trait. In the current sample, internal consistency, as assessed using Pearson’s correlation coefficients, was good for neuroticism ( $r = .47$ ) and extraversion ( $r = .45$ ), but weak for openness to experience ( $r = .20$ ), conscientiousness ( $r = .22$ ) and agreeableness ( $r = .24$ ). However, such low values are not uncommon for 2-item scales.

### *Psychological Flexibility (Psy-Flex)*

The Psy-Flex questionnaire (Gloster et al., 2021) is a validated self-report measure designed to assess psychological flexibility, a core construct in Acceptance and Commitment Therapy (Hayes et al., 2006). The questionnaire comprises 6 items, each corresponding to one of the six cognitive processes or skills that comprise psychological flexibility (acceptance, defusion, present moment awareness, stable self-awareness, values, committed action). Each item is rated on a 7-point



Likert scale ranging from 1 (“Very seldom”) to 5 (“Very often”). In the current sample, the scale had good internal consistency (Cronbach’s  $\alpha = .85$ ).

#### *Stanford Expectations of Treatment Scale (SETS)*

The SETS (Younger et al., 2012) is a validated self-report measure designed to assess positive and negative treatment outcome expectancies. The scale consists of 6 items, with 3 items each for positive (e.g., “This treatment will be completely effective”) and negative (e.g., “I am nervous about the negative effects of this treatment”) expectations, rated on a 7-point Likert scale ranging from 1 (“Strongly disagree”) to 7 (“Strongly agree”). In the current sample, internal consistency was acceptable for the positive expectancy subscale (Cronbach’s  $\alpha = .71$ ) and good for the negative expectancy subscale (Cronbach’s  $\alpha = .88$ ).

#### *Two-Item PROMIS® Global Physical and Mental Health Scales (GPH-2 and GMH-2)*

The GPH-2 and GMH-2 scales (Hays et al., 2017) were used to assess global physical and mental health, respectively. Each item was rated on a 5-point Likert scale ranging from 1 (“Poor/Not at all”) to 5 (“Excellent/Completely”). Scores for the two physical health and two mental health items were aggregated, with higher scores indicating better physical and mental health. Internal consistency, as assessed using Pearson correlation coefficients, was good for physical health ( $r = .57$ ) and mental health ( $r = .64$ ).

#### *Duration of Chronic Back Pain*

Participants were asked to indicate how long they had been in pain due to chronic lower back pain on a scale: 1 = Less than 3 months, 2 = 3-6 months, 3 = 6 months- 1 year, 4 = 1-2 years, 5 = More than 2 years.

*Willingness to Participate in a Psychedelic Trial*

Participants were asked: “Psychedelic compounds such as psilocybin, the active ingredient in magic mushrooms, are being studied for many mental health conditions. If you were asked to participate in a study of psilocybin for chronic pain, would you be interested?”. Participants answered either yes or no.

**Statistical Analyses**

All analyses were performed using IBM SPSS Statistics (v. 29.0) and R (v. 4.0.2, R Core Team, 2020). We first computed Spearman’s correlations between all continuous and ordinal study variables. Next, we performed three different binary logistic regressions using the *glm* function from the *stats* package in R. The dependent variable was willingness to participate in a psychedelic trial (0 = not willing, 1 = willing). In the first model, predictors included the five personality traits. In the second model, predictors included psychological flexibility as well as positive and negative outcome expectations. We also added physical and mental health, the duration of pain, and demographic variables (age, gender, race, employment status, marital status) as control variables. In the third model, to identify the strongest predictors, we entered variables that were significant in the first two models (openness to experience, positive and negative expectancy) as predictors. All continuous predictors were standardized using the *scale* function prior to inclusion in the models.

Multicollinearity was evaluated using the variance inflation factor (VIF) by employing the *vif* function in the *usdm* package (Naimi et al., 2013). VIF remained well below 5 for all predictors and, as such, multicollinearity did not pose any issues (Field et al., 2012).

## RESULTS

### Descriptive Statistics

A total of 988 participants completed the first round of data collection, of whom 235 ( $M_{\text{age}} = 58.83$ ,  $SD_{\text{age}} = 15.28$ , range = 22–88 years) participated in the second round of data collection. Among these respondents, 34.5% identified as men, 63.4% as women, 1.7% as non-binary, and 0.4% as transgender. Regarding race and ethnicity, the majority identified as White/European American (85.3%) and Non-Hispanic/Non-Latino (90.3%) (see Table 1). 72.8% ( $n = 719$ ) of the respondents indicated willingness to participate in a psychedelic trial (see Table 2).

**Table 1**

#### *Demographics*

	<i>N (%)</i>	<i>M (SD)</i>	Theoretical Min-Max	Actual Min-Max
Age <sup>a</sup>		58.83 (15.28)		22-88
Gender <sup>b</sup>				
Male	80 (34.5%)			
Female	147 (63.4%)			
Non-binary	4 (1.7%)			
Transgender	1 (0.4%)			
Race <sup>c</sup>				
White/European American	197 (85.3%)			
Black/African-American	6 (2.6%)			
Asian/Asian American	6 (2.6%)			

American Indian/Alaska Native	1 (0.4%)
Other	20 (8.7%)
Unknown	1 (0.4%)
Ethnicity <sup>d</sup>	
Non-hispanic&Non-latino	204 (90.3%)
Hispanic/latino	13 (5.8%)
Unknown	7 (3.1%)
Other	2 (0.9%)
Marital status <sup>b</sup>	
Single	46 (19.8%)
Married	125 (53.9%)
Widowed	13 (5.6%)
Separated	6 (2.6%)
Divorced	28 (12.1%)
Unknown	1 (0.4%)
Life partner	13 (5.6%)
Employment status <sup>c</sup>	
Employed and currently working	58 (25.8%)
Not Employed	9 (4.0%)
Retired	83 (36.9%)
Employed and on leave	5 (2.2%)
Disabled	44 (19.6%)
Part-Time	17 (7.6%)
Student	5 (2.2%)
Other	4 (1.8%)

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<sup>a</sup>N = 227. <sup>b</sup>N = 232. <sup>c</sup>N = 231. <sup>d</sup>N = 226. <sup>e</sup>N = 228.

**Table 2***Descriptive Statistics*

	<i>N (%)</i>	<i>M (SD)</i>	Theoretical Min-Max	Actual Min-Max
Willingness to participate in a psychedelic trial				
Yes	719 (72.8%)			
No	269 (27.2%)			
Extraversion <sup>a</sup>		3.30 (1.09)	1-5	1-5
Agreeableness <sup>a</sup>		3.69 (0.93)	1-5	1-5
Conscientiousness <sup>a</sup>		4.25 (0.79)	1-5	1.5-5
Neuroticism <sup>a</sup>		2.88 (1.13)	1-5	1-5
Openness to experience <sup>a</sup>		3.73 (0.99)	1-5	1-5
Psychological flexibility <sup>b</sup>		24.48 (4.30)	6-30	8-30
Positive expectancy <sup>c</sup>		3.82 (1.13)	1-7	1-7
Negative expectancy <sup>c</sup>		3.50 (1.76)	1-7	1-7
Physical Health <sup>c</sup>		3.01 (0.97)	1-5	1-5
Mental Health <sup>c</sup>		3.40 (1.03)	1-5	1-5
Duration of pain <sup>d,e</sup>		4.74 (0.85)	1-5	1-5

<sup>a</sup>N = 988. <sup>b</sup>N = 233. <sup>c</sup>N = 234. <sup>d</sup>N = 230. <sup>e</sup>Scale: 1 = Less than 3 months, 2 = 3-6 months,

3 = 6 months- 1 year, 4 = 1-2 years, 5 = More than 2 years

**Correlations Between Variables**

The correlation analysis revealed significant associations among personality traits, psychological flexibility, and expectancy variables (see Table 3). Higher extraversion, agreeableness, conscientiousness, openness to experience, and psychological flexibility were positively

interrelated, whereas neuroticism correlated negatively with these factors. Positive expectancy showed modest positive correlations with adaptive traits like agreeableness and conscientiousness, while negative expectancy was modestly negatively associated with extraversion only. Openness to experience was not significantly associated with positive or negative expectancy.

**Table 3***Spearman Correlations Between Measures*

	1	2	3	4	5	6	7	8	9	10	11
1 Extraversion <sup>a</sup>											
2 Agreeableness <sup>a</sup>	.13***										
3 Conscientiousness <sup>a</sup>	.13***	.12***									
4 Neuroticism <sup>a</sup>	-.19***	-.26***	-.17**								
5 Openness to Experience <sup>a</sup>	.14***	-.06*	.06*	.03							
6 Psychological Flexibility <sup>b</sup>	.21**	.19**	.24***	-.36***	.20***						
7 Positive expectancy <sup>c</sup>	.12	.14**	.15*	-.01	.06	.10					
8 Negative expectancy <sup>c</sup>	-.17**	-.03	.001	-.01	-.12	-.05	-.37***				
9 Physical Health <sup>c</sup>	.09	.02	.08	-.06	.10	.24***	.14*	-.11			
10 Mental Health <sup>c</sup>	.27***	.19**	.06	-.28***	.21**	.53***	.15*	-.04	.56***		
11 Duration of pain	.05	-.01	.02	-.04	.03	.09	-.04	-.09	-.13*	-.10	
12 Age <sup>d</sup>	.04	.06	.06	.20**	-.01	.20**	-.07	.18**	.01	-.12	.17*

*Note.* Spearman correlations between variables using unstandardized mean or sum scores.

<sup>a</sup>N = 988. <sup>b</sup>N = 233. <sup>c</sup>N = 234. <sup>d</sup>N = 227.

### Relationship Between Personality Traits and Willingness to Participate in a Psychedelic Trial

A binary logistic regression analysis showed that only openness to experience was positively associated ( $\beta = 0.186$ ,  $p = 0.01$ ) with willingness to participate in a psychedelic trial (see Table 4). Repeating the model in the subsample of participants who completed the second round of data collection ( $N = 235$ ) yielded consistent results ( $\beta = 0.382$ ,  $p = 0.03$ ), with no notable changes observed (see Supplementary Table S1).

**Table 4**

*Logistic Regression Results: Personality Traits as Predictors of Willingness to Participate in a Psychedelic Trial ( $N = 988$ )*

Predictor	$\beta$	Odds Ratio	Lower CI	Upper CI	Std. Error	Z-value	p-value
Extraversion	0.047	1.049	-0.099	0.194	0.075	0.633	0.527
Agreeableness	-0.068	0.934	-0.218	0.080	0.076	-0.897	0.370
Conscientiousness	-0.072	0.930	-0.221	0.073	0.075	-0.965	0.335
Neuroticism	0.000	1.000	-0.150	0.150	0.076	-0.002	0.999
<b>Openness</b>	<b>0.186</b>	<b>1.204</b>	<b>0.045</b>	<b>0.328</b>	<b>0.072</b>	<b>2.579</b>	<b>0.010</b>

### Relationship Between Psychological Flexibility, Expectations, and Willingness to Participate in a Psychedelic Trial

Next, we investigated whether psychological flexibility, outcome expectations, physical and mental health, and demographic variables predicted willingness to participate in a psychedelic trial. The results revealed that positive and negative expectancy were the only significant predictors (see Table 5). Specifically, a greater expectancy of positive outcomes was associated

with an increased likelihood of willingness to participate ( $\beta = 0.669$ ,  $p = 0.005$ ), whereas a greater expectancy of negative outcomes was associated with a decreased likelihood of willingness to participate in a psychedelic trial ( $\beta = -0.852$ ,  $p = 0.001$ ).

**Table 5**

*Logistic Regression Results: Psychological Flexibility, Expectancy, Mental and Physical Health, and Demographic Variables as Predictors of Willingness to Participate in a Psychedelic Trial ( $N = 235$ )*

Predictor	Beta	Odds Ratio	Lower CI	Upper CI	Std. Error	Z-value	P-value
(Intercept)	1.535	4.640	-1.989	5.446	1.874	0.819	0.413
Psychological flexibility	-0.303	0.739	-0.869	0.222	0.276	-1.097	0.273
<b>Positive expectancy</b>	<b>0.669</b>	<b>1.953</b>	<b>0.206</b>	<b>1.158</b>	<b>0.241</b>	<b>2.779</b>	<b>0.005</b>
<b>Negative expectancy</b>	<b>-0.852</b>	<b>0.427</b>	<b>-1.391</b>	<b>-0.366</b>	<b>0.259</b>	<b>-3.283</b>	<b>0.001</b>
Physical health	0.043	1.044	-0.464	0.565	0.261	0.165	0.869
Mental health	0.153	1.165	-0.433	0.733	0.295	0.518	0.604
Duration of pain	0.037	1.037	-0.499	0.487	0.248	0.147	0.883
Age	-0.294	0.745	-0.802	0.188	0.251	-1.172	0.241
Gender	-0.045	0.956	-0.790	0.746	0.389	-0.116	0.908
Race	-0.088	0.916	-0.318	0.172	0.122	-0.719	0.472
Marital status	0.082	1.085	-0.039	0.361	0.134	0.610	0.542
Employment status	-0.021	0.979	-0.048	0.011	0.014	-1.541	0.123

### **Strongest Predictors of Willingness to Participate in a Psychedelic Trial**

A binary logistic regression including only previously identified significant predictors (openness to experience, positive expectancy, negative expectancy) showed that, when controlling for the



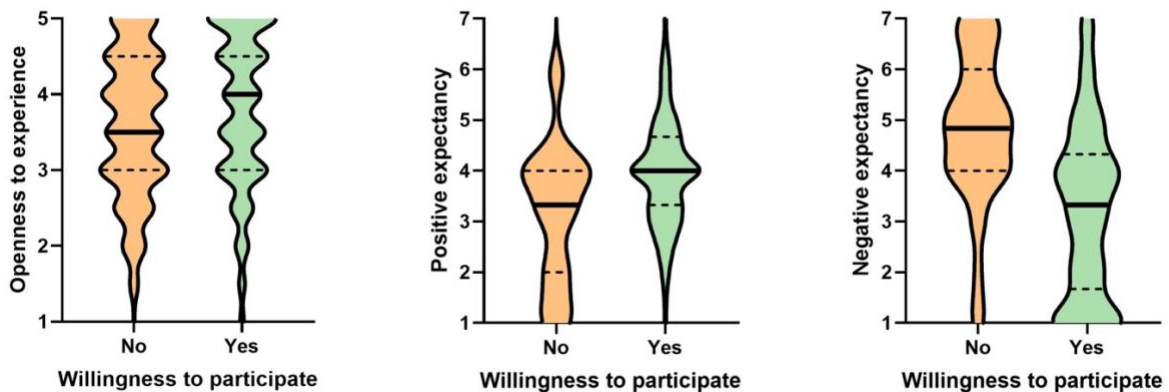
other predictors, negative expectancy remained the only significant predictor ( $\beta = -0.852$ ,  $p < 0.001$ ), with individuals who had higher negative expectancy being less willing to participate in a psychedelic trial (See Table 6 and Figure 1). After controlling for expectations, openness to experience was no longer significant ( $p = 0.061$ ).

**Table 6**

*Logistic Regression Results: Strongest Predictor of Willingness to Participate in a Psychedelic Trial*

Predictor	Beta	Odds Ratio	Lower CI	Upper CI	Std. Error	Z-value	P-value
Openness	0.350	1.419	-0.017	0.720	0.187	1.871	0.061
Positive expectancy	0.379	1.460	-0.029	0.797	0.210	1.807	0.071
<b>Negative expectancy</b>	<b>-0.852</b>	<b>0.427</b>	<b>-1.316</b>	<b>-0.429</b>	<b>0.225</b>	<b>-3.783</b>	<b>&lt;0.001</b>

**Figure 1**



**Fig.1** Violin plots illustrating differences in the (a) personality trait openness to experience, (b) positive expectancy, and (c) negative expectancy based on willingness to participate in a psychedelic trial. The thick solid lines indicate median values, dashed lines represent quartiles.

## DISCUSSION

In a cohort of chronic back pain patients, this study examined whether pre-existing participant characteristics, specifically personality traits, psychological flexibility, and outcome expectations, predict willingness to participate in a psychedelic trial. Overall, two thirds (73%) of participants expressed interest in taking part in a psychedelic trial. Among the Big Five personality traits, only openness to experience was associated with willingness to participate. Additionally, positive outcome expectations increased the likelihood of participation, while negative expectations decreased it. However, when all variables were considered together, negative expectancy emerged as the strongest and only significant predictor, suggesting that expectations, rather than personality traits, play a more central role in shaping willingness to participate in psychedelic research.

The present results corroborate concerns around the impact of expectation biases on psychedelic research in light of the proliferation of overly positive media narratives (Aday et al., 2022; Szigeti & Heifets, 2024). Such narratives may exacerbate placebo effects—where positive expectations amplify perceived therapeutic benefits—and simultaneously heighten the risk of nocebo effects, wherein unmet expectations or negative preconceptions elicit adverse psychological or physiological outcomes. Despite these considerations, the systematic evaluation of expectancy effects in psychedelic clinical trials remains limited, produce inconsistent results, and focus on the impacts of insufficient blinding integrity on study outcomes (Szigeti & Heifets, 2024). Thus, there is a critical gap in understanding how pre-treatment expectations affect participant recruitment and enrollment. The observed relationship between negative expectancy and reduced willingness to participate in psychedelic trials may introduce self-selection bias into

psychedelic trials, inflating efficacy estimates and limiting generalizability of results to broader populations.

The current results also provide some support for existing research on personality and psychedelics. While there is evidence suggesting that psychedelic use leads to increased openness, and that higher openness is associated with more positive psychedelic experiences and enhanced therapeutic outcomes (e.g. Aday et al., 2021; Bouso et al., 2018; Erritzoe et al., 2018; Pagni et al., 2025; Vizeli et al., 2024; Wagner et al., 2017), only a couple of studies have explored personality as a predictor of willingness to take psychedelics. These studies suggest a bidirectional relationship wherein openness not only predisposes individuals to psychedelic use but is also further enhanced by such experiences (Sjöström et al., 2024; Weiss et al., 2023), but focus exclusively on recreational contexts, contrasting with the present study which explores personality as a predictor of willingness to take psychedelics in a clinical setting.

To address these concerns, future research ought to longitudinally employ validated, standardized measures of these factors (Szigeti & Heifets, 2024). Future research should also aim to manage participant expectations by providing balanced narratives around psychedelics which present the uncertainties regarding treatment efficacy, rather than focusing solely on potential benefits (Aday et al., 2022). Future studies may also strive to enroll more representative samples consisting of participants with diverse expectations and personality traits. However, recruiting individuals with neutral and negative expectations or low openness poses a significant challenge. Thus, while the present results underscore the need for greater consideration of pre-treatment expectancy effects and personality traits in psychedelic trials, developing effective and ethical methodologies to investigate this phenomenon remains an ongoing challenge (Barber & Dike, 2023; Robinson et al., 2024; Smith & Appelbaum, 2022).

The results of this study should be considered in light of several limitations. First, the study population was restricted to a cohort of chronic back pain patients, which may limit the generalizability of the findings to broader populations. Second, while demographic variables were not significantly associated with willingness to participate, the sample was predominantly White (85%), precluding the generalization of results to more racially and ethnically diverse populations. Future research should prioritize the enrollment of more diverse samples to enhance the representativeness of study outcomes. Third, this study utilized the abbreviated Big Five Inventory (BFI-10), which may have compromised the reliability and validity of personality data (Rammstedt & John, 2007). Future studies should adopt a set of standardized personality measures to enable a more thorough assessment of personality's role in willingness and improve cross-study comparability. Finally, the voluntary nature of survey participation may itself have introduced a self-selection bias, as individuals who chose to invest time and effort in completing the surveys may differ systematically from those who chose not to participate. Additionally, participant attrition represents a limitation of this study, as a subset of participants who completed the initial data collection phase did not complete the subsequent phase. However, comparative analysis of the data obtained from the full sample ( $n = 988$ ) and the subset who completed all measures ( $n = 235$ ) revealed consistent results (see Table S1), suggesting that the impact of attrition on the overall findings was minimal.

In summary, among chronic back pain patients, openness to experience and positive outcome expectations were linked with greater willingness to participate in psychedelic trials, while negative outcome expectations were linked to lower willingness, emerging as the strongest predictor overall. These findings suggest that psychedelic research may be biased by the overrepresentation of individuals with positive expectations and associated placebo effects,

potentially inflating estimates of treatment efficacy and limiting generalizability to broader clinical populations. Further studies are needed to elucidate how pre-existing participant characteristics may explain trial enrollment and treatment outcomes.

## **ETHICS**

All procedures were reviewed and approved by the Stanford University Institutional Review Board (IRB #64474) and carried out in accordance with the Declaration of Helsinki.

All participants provided a written electronic informed consent, which outlined the study's purpose, procedures, rights, and potential risks and benefits. Consent was obtained by participants acknowledging their understanding and agreement before proceeding with the survey.

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## SUPPLEMENTARY MATERIALS

**Table S1**

*Logistic Regression Results: Personality Traits as Predictors of Willingness to Participate in a Psychedelic Trial in the Follow-Up Sample (N = 235)*

Predictor	Beta	Odds Ratio	Lower CI	Upper CI	Std. Error	Z-value	P-value
Extraversion	0.029	1.029	-0.333	0.392	0.184	0.156	0.876
Agreeableness	0.009	1.009	-0.369	0.377	0.189	0.045	0.964
Conscientiousness	0.018	1.018	-0.355	0.362	0.181	0.100	0.920
Neuroticism	0.083	1.086	-0.290	0.463	0.191	0.431	0.666
<b>Openness</b>	<b>0.382</b>	<b>1.465</b>	<b>0.038</b>	<b>0.730</b>	<b>0.175</b>	<b>2.177</b>	<b>0.030</b>

