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Analysis

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Psilocybin-assisted psychotherapy improves psychiatric symptoms across multiple dimensions in patients with cancer

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Psilocybin-assisted psychotherapy (PAP) has shown promise in treating mood and anxiety disorders in patients with cancer. However, patients with cancer often suffer from more than just depression and anxiety, and so far, PAP's effect on other psychiatric symptoms remains largely unknown. To address this gap, we pooled previously unpublished data from two phase II, randomized, placebo-controlled crossover trials involving 79 participants with cancer-related distress and analyzed PAP's effect on 9 psychiatric symptom dimensions: anxiety, depression, interpersonal sensitivity, hostility, obsession–compulsion, somatization, phobia, paranoia and psychosis. PAP significantly improved anxiety, depression, interpersonal sensitivity, hostility, obsession–compulsion and somatization without inducing any lasting phobia, paranoia or psychosis. Clinical improvements were consistent between trials. Together, our findings suggest that PAP has the potential to be a comprehensive mental health treatment for patients with cancer.

Patients with cancer face a range of mental health challenges including anxiety, depression, interpersonal sensitivity, hostility, somatization and obsessiveness[1,2]. The overall prevalence of psychiatric distress in this population has been estimated to range between 35% (ref. 2) and 65% (ref. 3), with anxiety and depression being among the most commonly reported symptoms[2,4]. Patients with cancer who are experiencing anxiety and depression are more likely to report increased pain, fatigue and impaired functioning, all of which can drastically diminish quality of life and worsen clinical outcomes[4–6]. Interpersonal sensitivity, defined as an individual's vulnerability to criticism and rejection, is heightened in patients with cancer and can contribute to poor self-image, social withdrawal and emotional distress[1,7]. The physical discomfort caused by cancer and the stress associated with undergoing treatment can contribute to irritability and hostility, which have been linked to worsening social support and decreased quality of life[1,8]. Somatization, the experience of physical symptoms that are not fully explained by the cancer or treatment, affects up to 30% of patients with cancer, with the highest incidence in those undergoing aggressive treatments or suffering from chronic pain[2,9]. Obsessiveness in patients with cancer is often characterized by excessive worrying or rumination about their prognosis, treatment options, side effects of medications and fear of recurrence, affecting approximately 17% of patients[2].

Therapy, particularly cognitive behavioral therapy, is often considered first-line for treating affective symptoms in patients with cancer[10]. This approach helps patients address negative thought patterns that contribute to emotional distress and develop healthier coping strategies as

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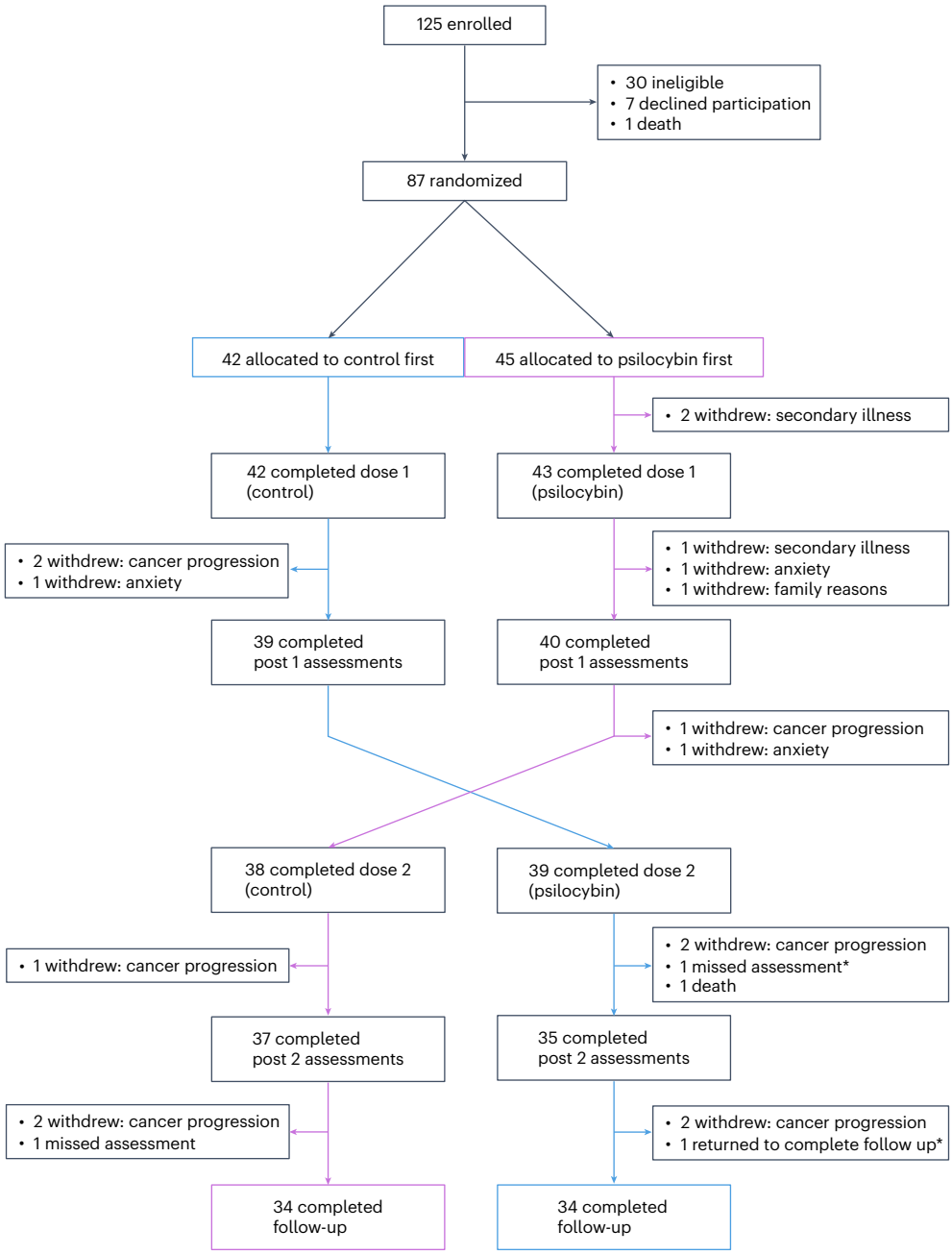

Fig. 1 | Pooled flow diagram of participants across both clinical trials. Out of the 125 participants enrolled, 87 met eligibility criteria and were randomized to receive either the control first or psilocybin first, followed by a cross-over. Seventy-nine participants completed the first medication session and post 1 assessments. Seventy-two participants completed the second medication session and post 2 assessments. A total of 68 participants completed follow-up. The reasons for participant drop-out are displayed in the panels adjacent to the flow diagram. The asterisk denotes that the same participant who missed post 2 assessments returned to complete follow-up.

well as behaviors for better stress management[11]. Support groups also offer an environment where patients can openly discuss their fears, anxieties and concerns related to their illness, fostering emotional resilience and psychological well-being[12,13]. Nonetheless, the efficacy of psychosocial interventions alone can be limited, especially in later stages of the disease when the psychological burden of cancer is profound[14].

In such instances, therapy is often combined with pharmacological treatments, including antidepressants, stimulants and ketamine[10]. Antidepressants such as selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors and mirtazapine are often considered first-line medications. However, these drugs can take weeks to take effect, have drug–drug interactions, cause considerable side effects and show limited efficacy in patients with cancer[15]. Stimulants, particularly methylphenidate, are commonly used for patients with late-stage cancers and in palliative care[16]. Stimulants rapidly improve mood, energy and cognition, while countering opioid-related sedation[17]. However, their use is associated with insomnia, palpitations, reduced appetite and cardiac decompensation, which limit their use[16]. More recently, ketamine is being investigated in patients with cancer for its rapid-acting antidepressant and analgesic properties[18,19]. However, ketamine can cause dissociation, confusion, cardiovascular side effects and more, which hinders its implementation[19]. Moreover, the benefits of ketamine treatment appear to be short-lived[18,20], necessitating frequent administrations.

A promising alternative to current standard of care for cancer-related psychiatric distress, with fewer side effects and more robust,

long-lasting treatment potential, is psychedelic-assisted psychotherapy. From the 1960s to the early 1970s, clinical studies involving the treatment of patients with cancer using classic psychedelics, predominantly lysergic acid diethylamide, suggested clinical efficacy for reducing pain, anxiety, depression and fear of death[21]. However, the widespread recreational use of psychedelics and the subsequent cultural upheaval of the 1960s led to the passage of the Controlled Substances Act in 1970, which effectively put a halt to all clinical studies with psychedelics by the mid 1970s[21]. Following a two-decade hiatus, human research with psychedelics gradually resumed in healthy volunteers and eventually in clinical populations[22].

In 2016, two phase II, randomized, placebo-controlled crossover trials were published suggesting rapid, robust and sustained decreases in anxiety and depression in patients with cancer-related psychiatric distress following a single session of psilocybin-assisted psychotherapy (PAP): Ross et al.[23] and Griffiths et al.[24]. However, an analysis of PAP's effect on psychiatric symptoms beyond anxiety and depression was not performed. Given the diversity of clinical applications for which psilocybin is currently being investigated for, including major depressive disorder[25,26], substance use disorders[27,28], obsessive–compulsive disorder[29], body dysmorphic disorder[30] and eating disorders[31], we hypothesized that PAP would impart multidimensional psychiatric improvements in patients with cancer. To test this hypothesis, we pooled previously unpublished data from the Brief Symptom Inventory (BSI)[32], which was collected in both aforementioned clinical trials, to analyze the effect of PAP on nine psychiatric symptom dimensions: (1) anxiety, (2) depression, (3) interpersonal sensitivity, (4) hostility, (5) obsession–compulsion, (6) somatization, (7) phobia, (8) paranoia and (9) psychosis.

Results

Participants

A combined total of 87 participants were randomized to receive either psilocybin first (n = 45) or control first (n = 42), followed by a crossover. Data were obtained through 6 months of follow-up from 68 participants, of whom 34 were in the group that received psilocybin first and 34 were in the group that received control first (Fig. 1). The demographic and clinical characteristics of participants who completed at least post-dose 1 assessments (n = 79) are provided in Table 1. Of these 79 participants, 42 were female and 37 were male, with an average age of 55.6 years. Seventy-three participants identified as white (92.4%), two as Black (2.5%), one as East Asian (1.3%) and three as other (3.8%). Most participants had an undergraduate degree or higher (91.1%) and were married, partnered or living together (64.6%). Fifty participants (63.5%) had advanced (stage III or IV), metastatic or recurrent cancers.

Table 1 | Pooled demographic and clinical characteristics of participants across both clinical trials

	Control first (n=39)	Psilocybin first (n=40)	All participants (n=79)
Age, years (mean)	57.8	54.9	55.6
Sex			
Male	17 (43.6%)	20 (50.0%)	37 (46.8%)
Female	22 (56.4%)	20 (50.0%)	42 (53.2%)
Race			
White	35 (90.0%)	38 (95.0%)	73 (92.4%)
Black	1 (2.5%)	1 (2.5%)	2 (2.5%)
East Asian	1 (2.5%)	0 (0.0%)	1 (1.3%)
Native American	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (5.0%)	1 (2.5%)	3 (3.8%)
Education			
Some high school	0 (0.0%)	1 (2.5%)	1 (1.3%)
High school diploma	2 (5.0%)	0 (0.0%)	2 (2.5%)
Some college	3 (7.5%)	1 (2.5%)	4 (5.1%)
Undergraduate degree	12 (31.0%)	20 (50.0%)	32 (40.5%)
Graduate or professional degree	22 (56.5%)	18 (45.0%)	40 (50.6%)
Relationship status			
Married, partnered, living together	25 (64.1%)	26 (65.0%)	51 (64.6%)
Single, divorced, widowed	14 (35.9%)	14 (35.0%)	28 (35.4%)
Prior hallucinogen use (% yes)	22 (56.4%)	16 (40.0%)	38 (48.1%)
Cancer stage			
Stage I or II, possibility for recurrence	12 (30.8%)	17 (42.5%)	29 (36.5%)
Stage III or IV, metastatic or recurrent	27 (69.2%)	23 (57.5%)	50 (63.5%)

Multidimensional effects of PAP

PAP significantly improved anxiety ($F_{1,155.3}$ = 8.16, P = 0.0049, Hedge's g = 0.64), depression ($F_{1,142.8}$ = 12.03, P = 0.0007, Hedge's g = 0.77), interpersonal sensitivity ($F_{1,150.7}$ = 12.60, P = 0.0005, Hedge's g = 0.79), obsession–compulsion ($F_{1,141.0}$ = 15.08, P = 0.0002, Hedge's g = 0.86), hostility ($F_{1,123.4}$ = 7.05, P = 0.0090, Hedge's g = 0.59) and somatization ($F_{1,157.1}$ = 19.32, P < 0.0001, Hedge's g = 0.98) as measured between groups before crossover at post-dose 1. Improvements in these six dimensions remained significant after correcting for multiple comparisons using the Holm–Bonferroni method to control the family-wise error rate at α = 0.05 (Supplementary Table 1). Following crossover, between-group differences lessened and were no longer significantly different at 6-month follow-up for all aforementioned dimensions (Fig. 2a).

For anxiety, depression, interpersonal sensitivity, hostility, obsession–compulsion and somatization, significant within-group improvements were observed in the psilocybin-first group for each assessment time point compared with baseline. By post-dose 2, significant within-group improvements were observed in the control-first group relative to baseline for these same six dimensions. These within-group improvements lasted through 6 months of follow-up for the control-first group for all aforementioned dimensions except somatization (Fig. 2a). PAP-related changes in anxiety, depression, interpersonal sensitivity, hostility, obsession–compulsion and somatization were highly consistent between clinical sites (Supplementary Fig. 1). The placebo (that is, nonpsychedelic) response was also highly consistent between clinical sites for these dimensions (Supplementary Fig. 2). PAP did not induce any lasting paranoia, phobia or psychosis (Fig. 2b).

Discussion

PAP has emerged as a promising treatment for psychiatric and existential distress in patients with cancer. While prior studies examined psilocybin's effect on affective symptoms[21], this study demonstrates PAP's multidimensional potential for ameliorating psychiatric symptoms beyond anxiety and depression in patients with cancer. Furthermore, PAP did not induce any lasting paranoia, phobia or psychosis, adding further evidence that psilocybin can be safely administered following rigorous screening under close medical supervision. Unlike current medications approved by the United States Food and Drug Administration, psilocybin has transient side effects[23,24], has minimal drug interactions[33] and appears to improve a broad spectrum of cancer-related psychiatric symptoms following a single medication session when paired with psychotherapy.

Psilocybin's multidimensional effects may be attributable to its action on the serotonin 2A (5-HT_{2A}) receptor[34]. This receptor has been implicated in various psychiatric disorders and is widely distributed

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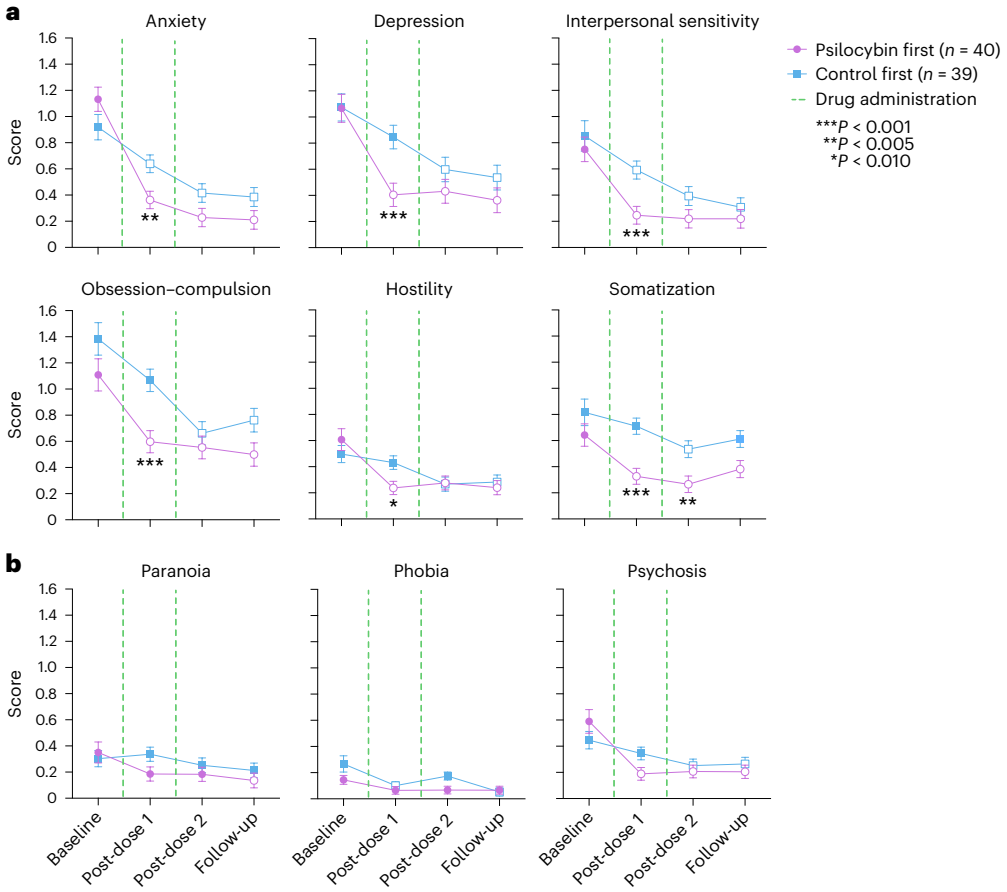

Fig. 2 | Multidimensional effects of PAP. Mean (±s.e.m.) estimates for every dimension of the BSI are presented at each time point, derived from mixed-effects models for repeated measures with compound symmetry covariance structures and fixed baseline covariates. Circular data points in purple represent the group means for participants who received psilocybin first ($n = 40$), while square data points in blue represent the group means for participants who received control first ($n = 39$). Pairwise comparisons assessed between-group differences at each time point using two-tailed F tests. The primary outcome measure was the difference in psychiatric symptoms between groups before crossover, assessed at post-dose 1. The Holm–Bonferroni method was used to control the family-wise error rate at $\alpha = 0.05$. The asterisks denote significant between-group differences. Within each group, differences in psychiatric symptoms were assessed at each time point compared with baseline using Tukey's post-hoc test. The open symbols indicate significant ($P < 0.05$) within-group differences from baseline. **a**, PAP significantly improved anxiety ($F_{1,155.3} = 8.16$, $P = 0.0049$), depression ($F_{1,142.8} = 12.03$, $P = 0.0007$), interpersonal sensitivity ($F_{1,150.7} = 12.60$, $P = 0.0005$), obsession–compulsion ($F_{1,141.0} = 15.08$, $P = 0.0002$), hostility ($F_{1,123.4} = 7.05$, $P = 0.0090$) and somatization ($F_{1,157.1} = 19.32$, $P < 0.0001$) as measured between groups before crossover. **b**, PAP did not induce any lasting paranoia, phobia or psychosis.

throughout the brain, particularly in areas involved in mood regulation, cognition and perception[35,36]. By agonizing the 5-HT_{2A} receptor, psilocybin acutely desynchronizes neural activity[37], resulting in brain networks[38] with diminished within-network integration and reduced between-network segregation[39]. Psilocybin-induced disruptions in the default mode network[40], a brain network associated with self-referential thinking and rumination[41], have been correlated with the intensity of the psychedelic experience[42] as well as antidepressant response to psilocybin[43]. In addition, psychedelics have been shown to enhance neuroplasticity and promote synaptogenesis[44,45], potentially facilitating adaptive changes in brain function that may underlie long-term symptom improvement[46,47].

The effects of psilocybin may also be attributable to the profound psycho-spiritual experiences that are commonly occasioned during dosing sessions[21,48]. In support of this, intensity of mystical-type experience was found to partially mediate the antidepressant and anxiolytic effects of psilocybin in both clinical trials used in this Analysis[23,24]. Moreover, qualitative research of PAP in patients with cancer has shown that psilocybin-induced mystical experiences are frequently interpreted through a spiritual or religious framework and that these subjective experiences help patients cope with existential distress, reduce fear of death and find meaning in the face of cancer[49,50]. In a 4.5-year follow-up of one of the trials used in this Analysis[23], surviving patients with cancer endorsed sustained improvements in anxiety, depression and existential distress[46]. These patients overwhelmingly attributed their positive life changes to PAP, rating it among the most personally meaningful and spiritually profound experiences of their lives.

More broadly, we speculate that the benefits of PAP may be generalizable to patients without cancer who suffer from obsessive–compulsive spectrum disorders and somatoform disorders. In fact, pilot studies suggest that PAP may be beneficial in the treatment of obsessive–compulsive disorder[29] and body dysmorphic disorder[30], an obsessive–compulsive spectrum disorder. Furthermore, reduced somatization could benefit patients with somatic symptom disorders and illness anxiety disorder.

Strengths and limitations

A strength of this Analysis is its derivation from two phase II, randomized, placebo-controlled crossover clinical trials that used nearly identical methods, allowing for effective data pooling. Moreover, both parent trials had nearly 80% participant retention through 6 months of follow-up and highly consistent results.

However, there are some limitations: (1) the pooled sample of participants consisted largely of white patients, which limits the

generalizability of the results; (2) there was a high degree of functional unblinding in both parent trials, as most study therapists accurately guessed the drug administered[23] or the approximate drug dosing during medication sessions[24]; (3) almost half of the pooled sample had previous psychedelic experience, which may have biased the results; and (4) this study was conducted post-hoc, meaning future clinical trials will need to incorporate multidimensional psychiatric assessments in their statistical analysis plans to validate the multi-symptom treatment potential of psilocybin.

The high degree of functional unblinding in both parent trials and likely expectancy biases may have contributed to placebo and nocebo effects that overestimate treatment outcomes. Moreover, because psilocybin was administered in conjunction with talk therapy, it is possible that the psychotherapy, rather than the study medication, was responsible for the enduring multidimensional treatment effects. However, these challenges are not unique to psychedelic clinical trials and are present across many pharmaceutical studies[51]. Future clinical trials may be able to overcome some of these limitations by (1) using more robust psychoactive controls, such as stimulants or cannabinoids, (2) measuring expectancy biases before medication dosing, (3) employing independent raters to evaluate study outcomes and (4) using factorial study designs, which enable the simultaneous evaluation of more than one intervention, to distinguish the effect of talk therapy from that of the study medication.

Conclusion

Our Analysis demonstrates that PAP alleviates a wide range of psychiatric symptoms in patients with cancer. While larger clinical trials will ultimately be needed to validate these findings, our study suggests that PAP has the potential to be a comprehensive mental health treatment for patients with cancer.

Methods

Overview of selected studies

Two phase II clinical trials investigating the efficacy of PAP in treating clinically significant anxiety and/or depression in patients with cancer were selected for pooled analysis: Ross et al.[23] and Griffiths et al.[24]. Both studies received institutional review board approval from their respective institutions, New York University Grossman School of Medicine[23] and Johns Hopkins University[24], and were registered on ClinicalTrials.gov (NCT00957359)[23] and (NCT00465595)[24]. Written informed consent was obtained from all participants. Participants did not receive financial compensation for their involvement in the parent clinical trials but were reimbursed for travel and lodging expenses.

Both trials used a placebo-controlled crossover design, where participants were randomized into one of two medication dosing sequences: (1) high-dose psilocybin first (21 mg per 70 kg in Ross et al. or 22–30 mg per 70 kg in Griffiths et al.) and control second (250 mg of niacin in Ross et al. or a low (placebo-like) dose of psilocybin 1–3 mg per 70 kg in Griffiths et al.); or (2) control first, followed by high-dose psilocybin second. Psychotherapy preceded and followed each medication dosing session. A battery of rating scale data was collected throughout the duration of each trial, from baseline until approximately 6 months after the second medication session. Detailed methodological information on inclusion/exclusion criteria, medication session procedures and psychotherapy procedures has been previously published[23,24].

Blinding integrity of selected studies

In both trials, the investigators, research staff, study therapists and participants were blinded to the drug administration conditions. The randomization of patients to dosing sequences was managed by pharmacy staff, and blinding integrity was measured in both trials. In Ross et al.[23], blinding integrity was assessed by asking the study therapists to guess whether the participant received psilocybin or active placebo after each medication session. The therapists guessed correctly in 28 out of 29 participants (97%). In Griffiths et al.[24], blinding integrity was assessed by asking study therapists to guess the dose of drug administered on a 10 cm line from 0 (nothing at all) to 10 (very high). The therapist ratings of medication dosing were significantly higher for the high-dose sessions of psilocybin, with a mean (±standard error of the mean (s.e.m.)) of 7.0 ± 0.3 versus 1.7 ± 0.2 for the low, placebo-like dose of psilocybin ($P < 0.001$). However, the distribution of ratings overlapped, with 12% of the low-dose sessions being rated >4 and 13% of the high-dose sessions being rated <4.

Rating scale overview and data pooling

The BSI is a 53-item questionnaire that uses a 5-point Likert scale from 0 ('not at all') to 4 ('extremely') to evaluate nine psychiatric symptom dimensions, namely, (1) anxiety, (2) depression, (3) interpersonal sensitivity, (4) hostility, (5) obsession–compulsion, (6) somatization, (7) paranoia, (8) phobia and (9) psychosis[32]. Scores for each dimension are calculated by averaging the ratings of corresponding questionnaire items. The BSI and its shorter variant, the BSI-18, have good psychometric properties[52] and are frequently used in psycho-oncology to quantify various dimensions of cancer-related distress[53]. Deidentified individual participant BSI data were collected from both parent trials and pooled at four time points that coincided closely between trials: (1) baseline, (2) post-dose 1 (5 weeks[24] and 6 weeks[23] after the first medication session), (3) post-dose 2 (5 weeks and 6 weeks after the second medication session) and (4) follow-up (6 months[24] and 6.5 months[23] after the second medication session). Seventy-nine participants (Ross et al. $n = 28$ and Griffiths et al. $n = 51$) completed the first medication session and post-dose 1 BSI. Seventy-two participants (Ross et al. $n = 23$ and Griffiths et al. $n = 49$) completed the second medication session and post-dose 2 BSI. Sixty-eight participants (Ross et al. $n = 23$ and Griffiths et al. $n = 45$) completed the 6-month follow-up BSI.

Statistical analysis

A mixed-effects repeated measures model using a compound symmetry covariance structure with fixed baseline covariates was conducted in SPSS version 21 for each dimension of the BSI. Pairwise comparisons assessed between-group differences at each time point using two-tailed F tests. The primary outcome measure was the difference in psychiatric symptoms between the two groups before crossover, assessed at post-dose 1. The Holm–Bonferroni method[54] was used to control the family-wise error rate at $\alpha = 0.05$. Effect sizes were calculated between groups using Hedge's g before crossover at post-dose 1. Within each group, psychiatric symptoms at each time point were compared with baseline using Tukey's post-hoc test with P values less than 0.05 considered statistically significant. The change in BSI scores was compared between the clinical sites of both trials following psilocybin and placebo medication sessions using two-tailed independent t-tests with P values less than 0.05 considered statistically significant.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The clinical trial participants of both studies used in this Analysis did not consent to the public sharing of their raw data. However, anonymized individual participant data can be made available provided the following conditions are met: (1) there is a data-sharing agreement and (2) an analysis plan in place. Upon data sharing, data can only be used for the specified purposes. Requests for data can be made by contacting the corresponding author.

Code availability

There was no custom code used in this Analysis.

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Author contributions

P.D.P. and S.R. conceived of the analysis. R.R.G. and S.R. provided deidentified individual participant data from their respective parent clinical trials. P.D.P. analyzed the data with support from J.G. and M.P.B. P.D.P., J.G., G.A.-L., C.J.K., R.J.Z., M.P.B., R.R.G. and S.R. interpreted the results of the analysis. P.D.P. wrote the paper. P.D.P., J.G., G.A.-L., C.J.K., R.J.Z, M.P.B., R.R.G. and S.R. critically revised the article.

Competing interests

R.J.Z. is a post-doctoral fellow in the NYU Langone Psychedelic Medicine Research Training program funded by MindMed. M.P.B. is principal investigator of the NYU Langone Center for Psychedelic Medicine Research Training Program, funded by MindMed. M.P.B. has received research funding from Tilray Canada, the Multidisciplinary Association for Psychedelic Studies (MAPS) PBC, B.More Inc., the Heffter Research Institute, the Turnbull Family Foundation, the Fournier Family Foundation, Dr. Bronner's Family Foundation, Bill Linton and the Riverstyx Foundation. M.P.B. serves on the Advisory Board of Ajna Labs LLC, Journey Colab and Bright Minds Biosciences, Inc. He is named as inventor on patent applications relating to the use of psilocybin for alcohol use disorder but has waived all rights and has no prospect of financial benefit. S.R. is the Director of NYU Langone Center for Psychedelic Medicine Research Training Program, which is funded by MindMed. S.R. currently receives, or has received in the past 36 months, grant support for clinical research from the National Institute on Drug Abuse (NIDA), National Cancer Institute (NCI), Heffter Research Institute, Usona Institute, Council on Spiritual Practices (CSP), Multidisciplinary Association of Psychedelic Studies (MAPS) and Reset Pharmaceuticals. S.R. is listed as a coinventor in two provisional patent applications (N420838US and N419987US) related to the use of psilocybin to treat psychiatric and existential distress in cancer. These provisional patent applications were filed by New York University Grossman School of Medicine and licensed by Reset Pharmaceuticals. S.R. has waived all rights in relation to these provisional patent applications and has no prospect of financial gain related to any future commercialization efforts related to these patents. The other authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Petros D. Petridis.

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☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	De-identified individual participant Brief Symptom Inventory (BSI) data were collected from both parent trials used in this pooled analysis. Data were stored using Microsoft Excel Version 16.
Data analysis	Data were analyzed using SPSS Version 21.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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The clinical trial participants of both studies used in this analysis did not consent to the public sharing of their raw data. However, anonymized individual participant data can be made available provided the following conditions are met: (1) there is a data-sharing agreement in place and (2) an analysis plan. Upon data sharing, data can only be used for the specified purposes. Requests for data can be made by contacting the corresponding author.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Please see Table 1 of the manuscript for the pooled demographic and clinical characteristics of participants across both trials. NYU Dataset (see Ross et al. 2016 J. Psychopharm) JHU Dataset (see Griffiths 2016 J. Psychopharm)
Reporting on race, ethnicity, or other socially relevant groupings	See above.
Population characteristics	See above.
Recruitment	NYU Study: Participants were recruited from a clinical cancer center at an academic medical facility (NYU Langone's Perlmutter Cancer Center). JHU Study: Participants were recruited through flyers, internet, and physician referral.
Ethics oversight	NYU Study: The study was approved and monitored by the institutional review board of the NYU School of Medicine. JHU Study: The study was approved and monitored by the institutional review board of Johns Hopkins. Informed consent was obtained from all participants in both parent clinical trials.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

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Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This is a pooled analysis using individual participant data derived from two previously published parent clinical trials: NYU Clinical Trial (see Ross et al. 2016 J. Psychopharm): Double-blind, placebo-controlled, crossover trial, comprised of 29 patients with cancer-related anxiety and depression were randomly assigned and received treatment with single-dose psilocybin (21 mg/70kg) or active control (niacin 250 mg), both in conjunction with psychotherapy. The primary outcomes were anxiety and depression assessed between groups prior to crossover. JHU Clinical Trial (see Griffiths et al. 2016 J. Psychopharm): Double-blind, placebo-controlled, crossover trial, comprised of 51 patients with life-threatening cancer causing symptoms of depression and/or anxiety were randomly assigned and received treatment with single dose psilocybin (22 or 30 mg/70 kg) or very low placebo-like dose of psilocybin (1 or 3 mg/70 kg). The primary outcomes were anxiety and depression assessed between groups prior to crossover. --- Deidentified individual participant BSI data was collected from both parent trials used in this analysis and pooled at 4 timepoints that coincided closely between trials: 1. Baseline; 2. Post-Dose 1 (5 weeks and 6 weeks after the first medication session); 3. Post-Dose 2 (5 weeks and 6 weeks after the second medication session); and 4. Follow-Up (6 months and 6.5 months after the second medication session). The data analyzed is quantitative data. A mixed-effects repeated measures model using a compound symmetry covariance structure with fixed baseline covariates was conducted in SPSS Version 21 for each dimension of the BSI. Pairwise comparisons assessed between-group differences at each timepoint using two-tailed F-tests. The primary outcome measure was the difference in psychiatric symptoms between the two groups prior to cross-over, assessed at post-dose 1. The Holm-Bonferroni method54 was used to control the family-wise error rate at alpha = 0.05. Effect sizes were calculated between groups using Hedge's g prior to crossover at post-dose 1. Within each group, psychiatric symptoms at each timepoint were compared to baseline using Tukey's post-hoc test with p-values less than 0.05 considered statistically significant. The change in BSI scores were compared between the clinical sites of both trials following psilocybin and placebo medication sessions using two-tailed independent t-tests with p-values less than 0.05 considered statistically significant.
Research sample	The aforementioned parent trials were selected for pooled analysis given their similarities in design, drug dosing, protocols, clinical populations studied, and rating scale measures collected. Please see below for more detailed information on the sample of

participants from both parent trials.

NYU Clinical Trial (see Ross et al. 2016 J. Psychopharm): Twenty-nine participants (18 F and 11 M), 56.3 average age, all had cancer (62% advanced, i.e. stage III or IV). All participants carried an anxiety-related diagnosis per the Structured Clinical Interview for DSM-IV with the majority meeting criteria for adjustment disorder (90%) and the rest for generalized anxiety disorder (10%).

JHU Clinical Trial (see Griffiths et al. 2016 J. Psychopharm): Fifty-one participants (25 F and 26 M), 56.3 average age, all had cancer (65% recurrent or metastatic). All participants carried a DSM-IV diagnosis: chronic adjustment disorder with anxiety (11), chronic adjustment disorder with mixed anxiety and depressed mood (11), dysthymic disorder (5), generalized anxiety disorder (GAD) (5), major depressive disorder (MDD) (14), or a dual diagnosis of GAD and MDD (4), or GAD and dysthymic disorder (1).

Sampling strategy

Both parent trials in the pooled analysis used convenience sampling.

NYU Clinical Trial (see Ross et al. 2016 J. Psychopharm): Participants were recruited from a clinical cancer center at an academic medical facility (NYU Langone's Perlmutter Cancer Center). Statistical power calculations were based on findings by Moreno and colleagues published in 2006 indicating that a sample size of 16 participants per group would provide 75% power to detect a reduction of 1 effect size and over 99% power to detect a reduction of 2 effect sizes at the 5% level.

JHU Clinical Trial (see Griffiths et al. 2016 J. Psychopharm): Participants were recruited through flyers, internet, and physician referral. Statistical power calculations were based on a specific outcome measure, the MEQ-30, for which the team had substantial psilocybin data from healthy volunteers.

Data collection

The lead author of the present study collected de-identified individual participant BSI data from the principal investigators of both parent clinical trials. Investigators and participants were blinded to study conditions during data collection of the parent clinical trials.

Timing

The lead author received de-identified individual participant data from the principal investigators of both parent clinical trials in July of 2022.

For timing of the parent clinical trials, please see below.

NYU Clinical Trial (see Ross et al. 2016 J. Psychopharm): Data were collected from 18 February 2009 to 22 October 2014 and the analysis was conducted from 3 November 2014 to 11 December 2015.

JHU Clinical Trial (see Griffiths et al. 2016 J. Psychopharm): Enrollment began October 2007 and final follow-up data were obtained in November 2014.

Data exclusions

No data were excluded from analysis.

Non-participation

Figure 1 depicts a pooled flow diagram of participants across both parent clinical trials used in this analysis along with reasons for participant dropout.

Randomization

Participants were allocated to groups randomly in both parent clinical trials. See below for more information.

NYU Clinical Trial (see Ross et al. 2016 J. Psychopharm): A blocked randomization methodology was employed to equally randomize participants to either the experimental or control groups. Randomization occurred by dosing sequence and did not stratify for any demographic or clinical characteristics. Robert Norman PhD (Biostatistician at the Bluestone Center for Clinical Research, NYU College of Dentistry) generated the randomization list. Within each block, subjects were randomly assigned to active drug or placebo. In total, there were 8 blocks comprised of 4 participants. This list included subject numbers sequentially starting from 1 on upwards and next to each number there was a description (psilocybin or placebo). The list was always kept with the study documents in a secure location. This design ensured that half of the participants received psilocybin first and that the other half received placebo first. The random allocation sequence was available only to administrative staff (Dr. Patricia Corby) at the Bluestone Center for Clinical Research. With each new participant, Dr. Corby (un-blinded) would consult the allocation sequence to determine what dosing sequence each particular participant would be randomized to. This information was given to un-blinded pharmacy staff to compound and prepare oral experimental drug or placebo in opaque (to preserve the blind), size 0 gelatin capsules.

JHU Clinical Trial (see Griffiths et al. 2016 J. Psychopharm): The randomization was managed by the research pharmacy. The investigators, research staff, and participants were blinded to the randomization sequence. The randomization schedule was generated with a random number table with the constraint that the same condition never occur more than three times consecutively.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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Clinical data

Policy information about clinical studies

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Clinical trial registration	NYU Clinical Trial (see Ross et al. 2016 J. Psychopharm): NCT00957359 JHU Clinical Trial (see Griffiths et al. 2016 J. Psychopharm): NCT00465595
Study protocol	NYU Clinical Trial: see Ross et al. 2016 J. Psychopharm and supplementary information JHU Clinical Trial: see Griffiths et al. 2016 J. Psychopharm and supplementary information
Data collection	The lead author of the present study collected de-identified individual participant BSI data from the principal investigators of both parent clinical trials.
Outcomes	The BSI was chosen for pooled analysis because it includes information on psychiatric symptoms beyond anxiety and depression.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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Supplementary information

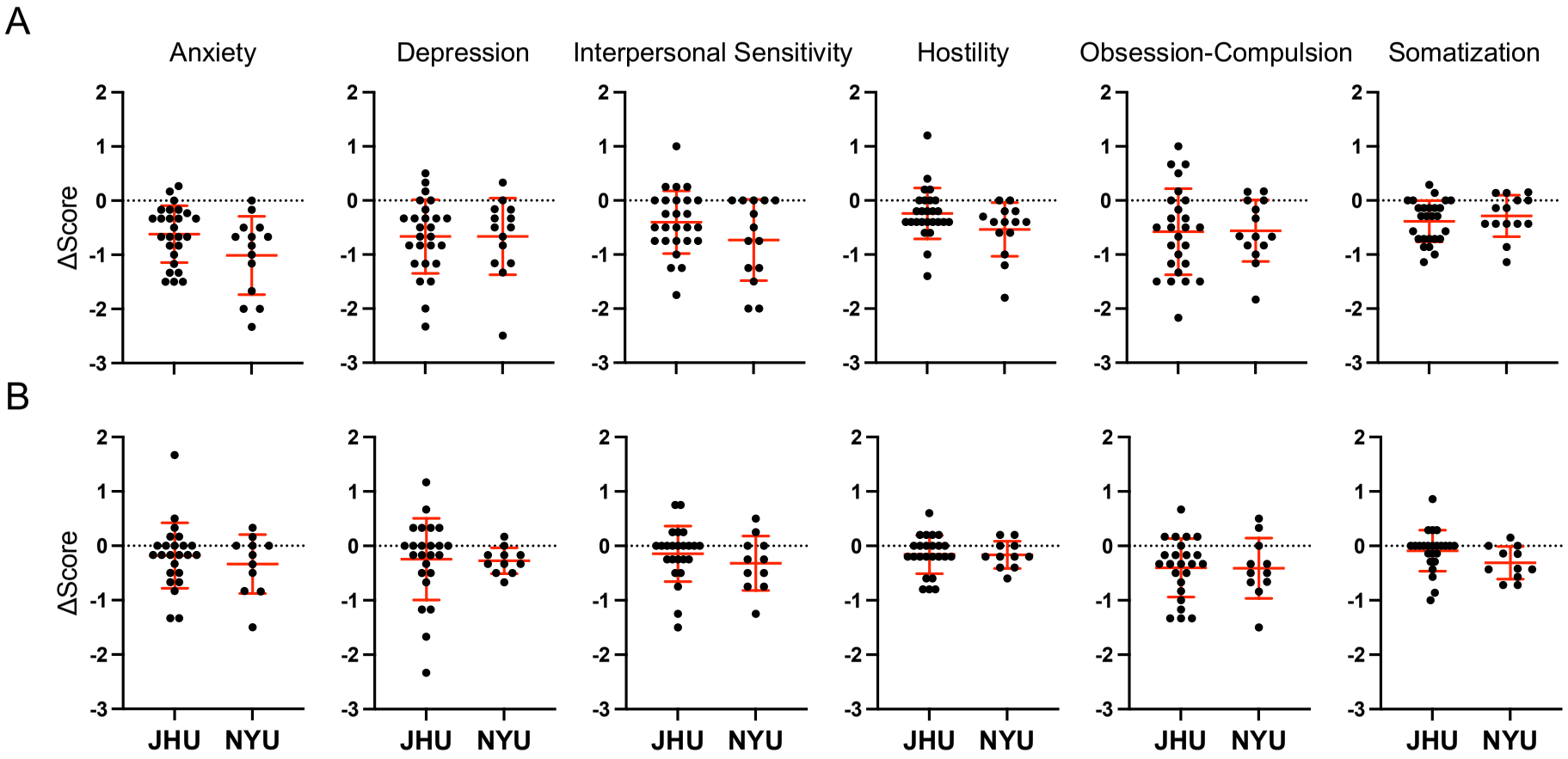
https://doi.org/10.1038/s44220-024-00331-0

Psilocybin-assisted psychotherapy improves psychiatric symptoms across multiple dimensions in patients with cancer

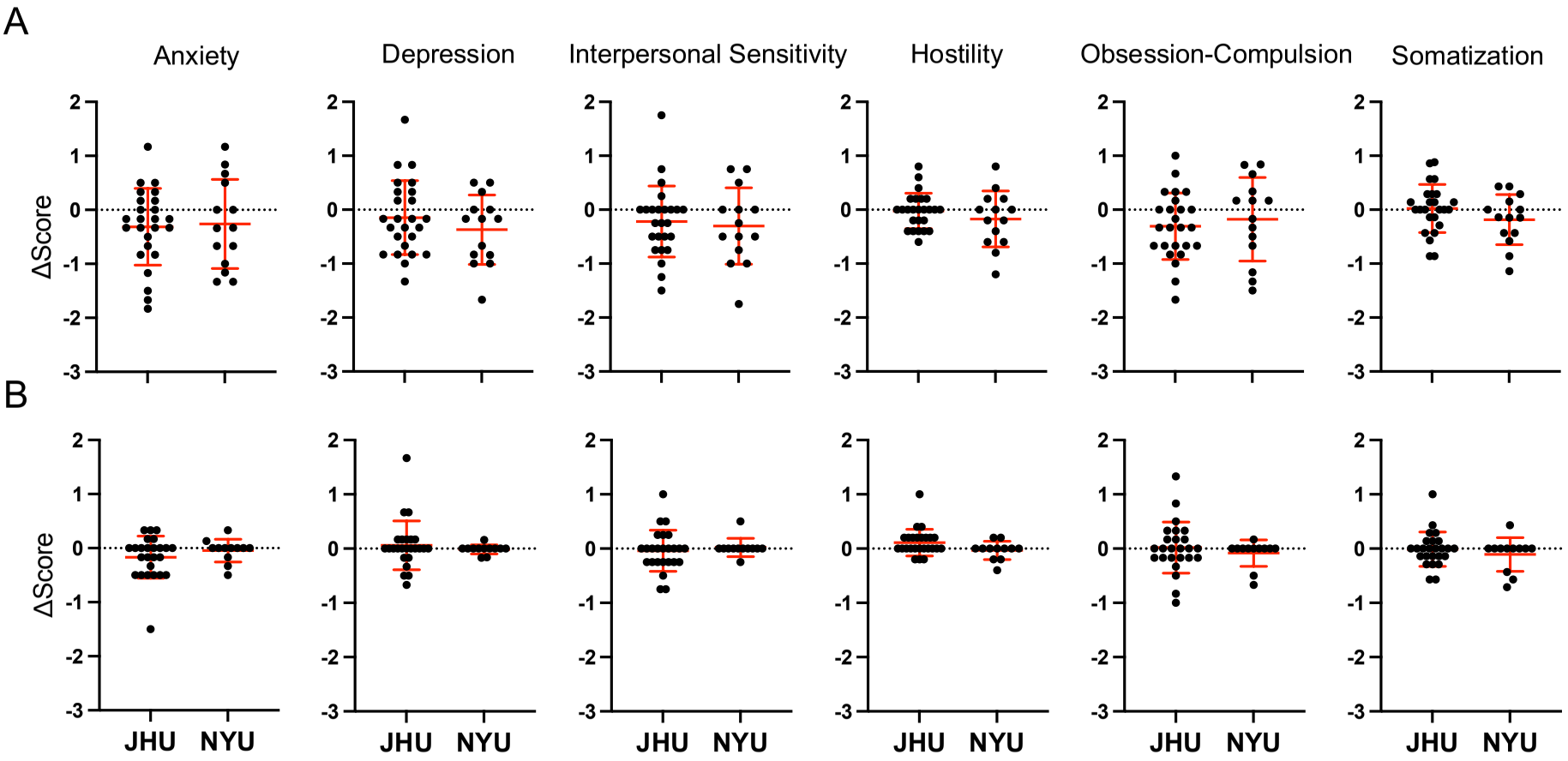
In the format provided by the authors and unedited

Experimental Hypothesis	F-Test Two-Tailed	Raw P-Value	Adjusted Significance Threshold	Decision on H_1
Somatization	19.32	<.0001	.05/9 = .005	Accept
Obsession-Compulsion	15.08	.0002	.05/8 = .006	Accept
Interpersonal Sensitivity	12.60	.0005	.05/7 = .007	Accept
Depression	12.03	.0007	.05/6 = .008	Accept
Anxiety	8.16	.0049	.05/5 = .010	Accept
Hostility	7.05	.0090	.05/4 = .012	Accept
Psychosis	5.14	.0250	.05/3 = .017	Reject
Paranoia	3.91	.0499	.05/2 = .025	Reject
Phobia	0.80	.3731	.05/1 = .050	Reject

Supplementary Table 1: Somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, and hostility remained significant after correcting for multiple comparisons using the Holm-Bonferroni method to control the family-wise error rate at $\alpha = 0.05$.



Supplementary Figure 1: Mean change (± SD) in Brief Symptom Inventory score on anxiety, depression, interpersonal sensitivity, hostility, obsession-compulsion, and somatization is shown in red for both clinical sites (JHU - Johns Hopkins University, clinical site for Griffiths *et al*. and NYU - New York University, clinical site for Ross *et al*.) following **(A)** the 1st psilocybin session (n = 26 JHU, n = 14 NYU) and **(B)** the 2nd psilocybin session (n = 24 JHU, n = 11 NYU). Two-tailed independent t-tests were used to compare change in BSI scores between clinical sites. There were no significant differences in response to PAP between clinical sites ($p > 0.05$).



Supplementary Figure 2: Mean change (± SD) in Brief Symptom Inventory score on anxiety, depression, interpersonal sensitivity, hostility, obsession-compulsion, and somatization is shown in red for both clinical sites (JHU - Johns Hopkins University, clinical site for Griffiths *et al*. and NYU - New York University, clinical site for Ross *et al*.) following **(A)** the 1st control session (n = 25 JHU, n = 14 NYU) and **(B)** the 2nd control session (n = 25 JHU, n = 12 NYU). Two-tailed independent t-tests were used to compare change in BSI scores between clinical sites. There were no significant differences in placebo (i.e. non-psychedelic) response between clinical sites ($p > 0.05$).