Journal of Affective Disorders 334 (2023) 100–112

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

How does psilocybin therapy work? An exploration of experiential avoidance as a putative mechanism of change

Richard J. Zeifman [a,b,c,*], Anne C. Wagner [a,d], Candice M. Monson [a], Robin L. Carhart-Harris [b,e]

[a] Department of Psychology, Toronto Metropolitan University, Toronto, Canada
[b] Centre for Psychedelic Research, Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, UK
[c] NYU Langone Centre for Psychedelic Medicine, Department of Psychiatry, NYU Grossman School of Medicine, New York, USA
[d] Remedy Institute, Toronto, Canada
[e] Psychedelics Division, Neuroscape, University of California, San Francisco, USA

ARTICLE INFO

Keywords:
Psilocybin therapy
Experiential avoidance
Mechanism of change
Major depressive disorder

ABSTRACT

Background: Psilocybin therapy is receiving attention as a mental health intervention with transdiagnostic potential. In line with psychotherapeutic research, qualitative research has highlighted the role of reductions in experiential avoidance (and increases in connectedness) within psilocybin therapy. However, no quantitative research has examined experiential avoidance as a mechanism underlying psilocybin therapy's therapeutic effects.

Method: Data was used from a double-blind randomized controlled trial that compared psilocybin therapy (two 25 mg psilocybin session plus daily placebo for six weeks) with escitalopram (two 1 mg psilocybin sessions plus 10–20 mg daily escitalopram for six weeks) among individuals with major depressive disorder ($N = 59$). All participants received psychological support. Experiential avoidance, connectedness, and treatment outcomes were measured at pre-treatment and at a 6 week primary endpoint. Acute psilocybin experiences and psychological insight were also measured.

Results: With psilocybin therapy, but not escitalopram, improvements in mental health outcomes (i.e., well-being, depression severity, suicidal ideation, and trait anxiety) occurred via reductions in experiential avoidance. Exploratory analyses suggested that improvements in mental health (except for suicidal ideation) via reduction in experiential avoidance were serially mediated through increases in connectedness. Additionally, experiences of ego dissolution and psychological insight predicted reductions in experiential avoidance following psilocybin therapy.

Limitations: Difficulties inferring temporal causality, maintaining blindness to condition, and reliance upon self-report.

Conclusions: These results provide support for the role of reduced experiential avoidance as a putative mechanism underlying psilocybin therapy's positive therapeutic outcomes. The present findings may help to tailor, refine, and optimize psilocybin therapy and its delivery.

> "I will fall in the void, fall in the void, just to avoid anything that can bring me down."
>
> Kid Cudi (2020)

> "I took away from the experience that I used to get angry about having anxiety, now I think I can have the anxiety, I can just feel it and it will go, I don't have to have the fear or run away."
>
> Watts et al., 2017. p. 541

A growing body of research provides support for psilocybin therapy (i.e., administration of the classic psychedelic psilocybin, a 5-HT_{2A} receptor agonist, alongside psychological support) as a novel mental health intervention. Although additional research remains necessary, these findings suggest that the positive effects of psilocybin therapy may extend across a range mental health outcomes, including anxious and depressive symptoms (Agin-Liebes et al., 2020; Carhart-Harris et al.,

* Corresponding author at: NYU Langone Centre for Psychedelic Medicine, Department of Psychiatry, NYU Grossman School of Medicine, 1 Park Avenue, 10016 New York, NY, USA.
E-mail address: richard.zeifman@nyulangone.org (R.J. Zeifman).

https://doi.org/10.1016/j.jad.2023.04.105
Received 21 November 2022; Received in revised form 17 April 2023; Accepted 28 April 2023
Available online 3 May 2023

2018a; Carhart-Harris et al., 2021; Davis et al., 2021a; Goodwin et al., 2022; Griffiths et al., 2016; Gukasyan et al., 2022; Ross et al., 2016), suicidal ideation (Carhart-Harris et al., 2018a; Carhart-Harris et al., 2021; Ross et al., 2021; Zeifman et al., 2022a), and well-being (Carhart-Harris et al., 2021). The wide range of mental health outcomes for which psilocybin therapy shows promise suggests that it may target underlying transdiagnostic mechanisms of change (i.e., how an intervention leads to improvement; Carhart-Harris and Friston, 2019; Carhart-Harris et al., 2023; Kočárová et al., 2021). However, limited research has yet to elucidate the specific mechanisms underlying psilocybin therapy's therapeutic effects. Not all individuals respond to psilocybin therapy; some experience a relapse in the weeks and months following treatment, and concerns exist regarding its cost-effectiveness (Davis et al., 2018; Nutt et al., 2020). Thus, elucidating psilocybin therapy's mechanisms of change will be essential for optimizing therapeutic outcomes, as well as guiding treatment development, refinement, and delivery (Kazdin, 2007). The goal of the present study was to examine reductions in experiential avoidance (i.e., unwillingness to remain in contact with distress and rigid engagement in behaviours to minimize distress; Gámez et al., 2014) as a potential mechanism of change underlying the therapeutic effects of psilocybin therapy.

A broad swathe of research suggests that experiential avoidance plays a key role in the onset, maintenance, and effective treatment across a range of mental health outcomes (Bullis et al., 2019; Sloan et al., 2017). For instance, across several psychotherapeutic interventions, reductions in experiential avoidance are predictive of improvements in depression severity (e.g., Jankowski et al., 2021; Østergaard et al., 2020), anxiety (e.g., Espejo et al., 2017; Eustis et al., 2020), suicidal ideation (e.g., Ellis and Rufino, 2016; Rufino and Ellis, 2018), and well-being (Jankowski et al., 2021; Yela et al., 2020). Several lines of research also point to the role of experiential avoidance as a putative mechanism within psilocybin therapy (for a discussion, see Wolff et al., 2020). Qualitative analyses of participant's experience within psilocybin therapy trials have highlighted the putative role of experiential avoidance (Agin-Liebes et al., 2021; Belser et al., 2017; Swift et al., 2017; Watts et al., 2017). For instance, among individuals that received psilocybin therapy for treatment-resistant depression, shifting from experiential avoidance to experiential acceptance, as well as from a sense of disconnectedness (from one's self, others, and the word) to connectedness were identified as key themes underlying therapeutic improvement (Watts et al., 2017). Similarly, among individuals with cancer-related distress who received psilocybin therapy "participants described how they came to surrender or 'let go,' leading from a defensive posture of emotional or psychological resistance to an accepting posture" (Belser et al., 2017, p. 379). Moreover, among AIDS survivors experiencing demoralization who received psilocybin therapy "all nine participants reported experiencing a newfound willingness to 'let go' and be open to vulnerable feelings such as sadness and grief" (Agin-Liebes et al., 2021, p. 11).

Within convenience samples, survey-based studies have similarly found that, following the use of a classic psychedelic, reductions in experiential avoidance are associated with improvements in mental health, including increases in positive affect (Agin-Liebes et al., 2022) and decreases in negative affect (Agin-Liebes et al., 2022), depression severity (Close et al., 2020; Zeifman et al., 2020), anxiety/depression severity (Davis et al., 2020a, 2020b), trauma-related symptoms (Davis et al., 2020b) and suicidal ideation (Zeifman et al., 2020). Several of these studies have also found that elements of the psychedelic experience (e.g., psychological insight) are predictive of these reductions in experiential avoidance (Agin-Liebes et al., 2022; Davis et al., 2020a, 2021b). However, the majority of studies with classic psychedelics have used measures of experiential avoidance (i.e., the Acceptance and Action Questionnaire [AAQ; Hayes et al., 2004] or the AAQ-II [Bond et al., 2011]) that have questionable validity (Tyndall et al., 2019). Moreover, all studies used non-clinical convenience samples of individuals with plans to use a classic psychedelic, did not use controlled designs, and none were focused on psilocybin therapy specifically.

Results from a recent randomized controlled trial (RCT) among individuals with major depressive disorder (MDD) found that, relative to escitalopram (a selective serotonin reuptake inhibitor [SSRI] and first line treatment for MDD; Cipriani et al., 2018), psilocybin therapy was associated with greater reductions in experiential avoidance (Carhart-Harris et al., 2021) and increases in connectedness (Watts et al., 2022). Furthermore, increases in connectedness were found to predict improvements in depression severity following psilocybin therapy (Watts et al., 2022). However, the relationship between reductions in experiential avoidance and improvements in mental health following psilocybin therapy has not yet been examined. Furthermore, quantitative research has not yet simultaneously examined the relationship between experiential avoidance and connectedness as putative mechanisms within psilocybin therapy. Additionally, research has not yet compared the role of experiential avoidance in mediating responses to psilocybin therapy versus its role in mediating responses to other interventions, such as a course of an SSRI. Such research is important for determining whether reductions in experiential avoidance is a unique mechanism underlying the therapeutic effects of psilocybin therapy (relative to other pharmacological interventions) and whether changes in experiential avoidance and therapeutic outcomes merely co-occur. Therefore, using data from Carhart-Harris et al.'s (2021) RCT, we examined the relationship between reductions in experiential avoidance and improvements in mental health following psilocybin therapy and escitalopram. We hypothesized that, following psilocybin therapy, improvements in mental health outcomes would occur via reductions in experiential avoidance. We also hypothesized that improvements in therapeutic outcomes via reductions in experiential avoidance would be significantly greater following psilocybin therapy condition relative to escitalopram. Exploratory analyses examined whether improvements in mental health via reductions in experiential avoidance occurred through increases in connectedness. Finally, elements of the psilocybin experience were examined as predictors of reductions in experiential avoidance.

1. Methods

1.1. Participants

This study included 59 individuals with MDD from Carhart-Harris et al.'s (2021) RCT. Inclusion criteria were: (a) presence of an MDD diagnosis given by a general medical practitioner; (b) confirmation of MDD diagnosis (per DSM-IV diagnostic criteria; American Psychiatric Association, 2000) based on assessment (Mini-International Neuropsychiatric Interview; Sheehan et al., 1998) by a study psychiatrist; (c) moderate to severe depression severity (17 on the Hamilton Rating Scale for Depression [HAM-D-17; Hamilton, 1960]); (d) 18–80 years of age; and (e) sufficient competency with the English language. Exclusion criteria were: (a) presence of MRI contraindications; (b) abnormal QT interval prolongation at screening or a history of abnormal QT; (c) presence of SSRI contraindications or contraindicated medications that the participant is unwilling to discontinue or would be medically inappropriate to discontinue; (d) current or past diagnosis of a psychotic disorder; (e) immediate family member with a diagnosed psychotic disorder; (f) medically significant condition rendering the participant inappropriate for the study due to safety concerns (e.g., diabetes, epilepsy, severe cardiovascular disease); (g) history of serious suicide attempts requiring hospitalization; (h) significant history of mania; (i) psychiatric condition or clinical presentation judged by study therapists to be incompatible with establishment of rapport with therapy team and/or safe exposure to psilocybin (e.g., borderline personality disorder); (j) blood or needle phobia; (k) positive pregnancy test at screening or during the study and individuals who are planning a pregnancy and/or nursing/breastfeeding; (l) unwillingness to use an acceptable contraceptive method throughout participation in the study; (m) current

drug or alcohol dependence; and (n) no email access.

1.2. Procedures

The study was a double-blind RCT (clinicaltrials.gov; NCT03429075). Individuals were randomly assigned to receive (a) two large doses of psilocybin (two 25 mg doses of psilocybin 3 weeks apart) and 6 weeks of daily inactive placebo (psilocybin therapy condition) or (b) two very low doses of psilocybin (1 mg dose of psilocybin twice separated by three weeks) and 6 weeks of daily escitalopram (10 mg for 3 weeks, followed by 20 mg for 3 weeks; escitalopram condition). Psilocybin was obtained from COMPASS Pathways. Escitalopram and placebo were obtained from the Pharmacy Manufacturing Unit of Guy's and St. Thomas's Hospital. The study was conducted at the Centre for Psychedelic Research at Imperial College London in the Department of Brain Sciences at Imperial College London. Research ethics for the study were received from the Brent Research Ethics Committee, the U.K. Medicines and Healthcare Products Regulatory Agency, the Health Research Authority, the Imperial College London Joint Research Compliance and General Data Protection Regulation Offices, and the National Institute for Health Research Imperial Clinical Research Facility. Additional approval for the analyses completed for the present manuscript was received from Toronto Metropolitan University's Research Ethics Board.

Participants were recruited via trial networks, patient databases, social media, online sources, and direct referral by general medical practitioners. Confirmation of participants' MDD diagnosis and medical history was obtained from their medical practitioner. Participants were then invited to an initial screen to determine eligibility. The screen was conducted by a study psychiatrist via video call and included administration of the HAM-D-17. Suitability for treatment was also assessed by two study therapists through a video call. Participants who remained eligible were invited to complete an in-person screen, where a psychiatrist reviewed the details from their phone screen, conducted an assessment to confirm their MDD diagnosis, screened for co-morbid psychiatric diagnoses, and conducted a physical examination and additional exams (i.e., ECG, urine drug testing, blood and pregnancy testing) to confirm their eligibility.

All participants received psychotherapeutic treatment (including preparation, psychological support during dosing sessions and integration sessions; see Carhart-Harris et al., 2021; Watts, 2021; Watts and Luoma, 2020). Primary goals of the preparation sessions were the development of therapeutic rapport (see Murphy et al., 2022), discussion of the importance of engaging with difficult emotions, and identifying therapeutic intentions for dosing sessions. Dosing sessions were conducted according to traditional guidelines for psilocybin therapy (Johnson et al., 2008). Sessions occurred in a dimly lit and comfortable room. To facilitate meaningful and therapeutically useful imagery and emotional experiences (see Kaelen et al., 2018), participants were provided with an eyeshade and encouraged to listen to a pre-set music playlist. Two therapists (or guides) were present throughout the dosing sessions. The only instructions during dosing sessions were gentle recommendations to "turn inward" and explore rather than avoid the emerging content of their experience, as well as to feel, rather than distract themselves from, bodily sensations. Participants were also encouraged to briefly communicate key experiential themes with their therapists with more interaction between the participant and therapist occurring toward the end of the dosing session as direct drug effects waned. Integration sessions were structured to help individuals putting together a narrative of their psilocybin experience, translate psychological insights from and since their dosing session into their day-to-day life, and behavioral change.

For study flow, see Supplementary Material (eFigure1). Prior to their first dosing session, participants competed two preparation sessions. On the day of their first psilocybin dosing session, participants received 6 weeks of capsules. Participants completed two integration sessions following their first dosing session and one additional preparation session prior to their second psilocybin dosing session, which was completed 3 weeks after their first dosing session. Participants then completed two additional integration sessions and their post-treatment assessment, which occurred 3 weeks after their second psilocybin dosing session. Measures of mental health outcomes (i.e., well-being, depression severity, suicidal ideation, and trait anxiety), experiential avoidance, and connectedness were completed pre-treatment (Visit #2) and post-treatment (Visit #7; i.e., 6 weeks after baseline). Measures of acute psilocybin experiences were completed 1 day after each dosing session and a measure of perceived increase in psychological insight was completed at post-treatment.

1.3. Measures

1.3.1. Demographics form and clinical characteristics

Participants completed demographic items, including age, gender, race, level of education, employment status, and previous psilocybin use. Clinical characteristics were collected by clinical interview, including duration of major depressive episode, as well as history of psychiatric medication history and psychotherapy.

1.3.2. Experiential avoidance

Experiential avoidance was measured using the Brief Experiential Avoidance Questionnaire (BEAQ; Gámez et al., 2014). The BEAQ is a 15-item self-report measure that includes items such as "The key to a good life is never feeling any pain" and "I work hard to keep out upset feelings." Participants rate the extent to which they agree with each item on a scale from 1 (strongly disagree) to 6 (strongly agree). One item is reverse-scored. The BEAQ has good internal consistency and discriminant validity (Gámez et al., 2014; Tyndall et al., 2019).

1.3.3. Well-being

Well-being was measured using the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; Tennant et al., 2007). The WEMWBS is a 14-item self-report measure of eudemonic and hedonic well-being, which includes items related to cognitive processes (e.g., "I've been thinking clearly"), feelings (e.g., "I've been feeling cheerful") and the quality of relationships with others (e.g., "I've been feeling close to other people"). Participants select the response that best describes their experience over the past 2 weeks on a scale from 1 ("None of the time") to 5 ("All of the time"). The WEMWBS has strong internal consistency and good construct validity (Tennant et al., 2007).

1.3.4. Depression severity

1.3.4.1. Montgomery-Åsberg Depression Rating Scale (MADRS). The MADRS (Montgomery and Åsberg, 1979) is a 10-item clinician-administered scale that assesses for the presence of affective, somatic, cognitive, and behavioral symptoms of depression. Items are scored on a scale from 0 to 6 and total scores range from 0 to 60 with the following severity ratings: 0–6 normal or absence of depression, 7–19 mild, 20–34 moderate, and $\geq$ 34 severe depression. The MADRS shows strong psychometric properties, including excellent internal consistency and construct validity (Carmody et al., 2006).

1.3.4.2. Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16). The QIDS-SR-16 (Rush et al., 2003) is a 16-item self-report measure that assesses the presence of the nine key diagnostically relevant symptoms of MDD over the previous 7 days. Items are rated on a scale from 0 to 3 with total scores range from 0 to 27 and the following severity ratings: 0–5 no depression, 6–10 mild, 11–15 moderate, 16–20 severe, and 21–27 very severe depression. The QIDS-SR-16 has good internal consistency and construct validity (Rush et al., 2003, 2006).

1.3.5. Suicidal ideation

Self-reported suicidal ideation was measured using the Suicidal Ideation Attributes Scale (SIDAS; Van Spijker et al., 2014). The SIDAS is a 5-item self-report measure of suicidal ideation that assesses the frequency, controllability, closeness to attempt, level of distress, and impact on daily functioning associated with suicidal thoughts. Items are rated on a scale from 0 (e.g., "never") to 10 (e.g., "always"), with one reverse scored item. The first item of the SIDAS is a screener item ("In the past month, how often have you had thoughts about suicide?") and individuals who respond with a 0 (i.e., "never") receive a total score of 0. The SIDAS has good to excellent internal consistency and convergent validity (Van Spijker et al., 2014).

1.3.6. Trait anxiety

Self-reported trait anxiety was measured using the trait anxiety scale of the State-Trait Anxiety Inventory (STAI-Trait; Spielberger, 1983). The STAI-Trait is a 20-item self-report measure of an individual's predisposition to experience anxiety in stressful situations. Items are rated on a Likert scale from 1 ("not at all") to 4 ("very much so"). The STAI-Trait has good psychometric properties, including strong internal consistency, concurrent validity, and test-retest reliability (Spielberger, 1983, 1989).

1.3.7. Connectedness

Connectedness was measured using the Watts Connectedness Scale (WCS; Watts et al., 2022). The WCS is a 19-item self-report measure of connectedness to (a) one's self (6 items; e.g., "I have been able to fully experience emotion, whether positive or negative"), (b) others (6 items; e.g., "I have felt alone"), and (c) the world (7 items; e.g., "I have felt connected to all humanity"). Participants rate the extent to which they agree with each item on a visual analogue scale from 0 ("Not at all") to 100 ("Entirely"). Four items are reverse-scored. The WCS has good internal consistency and has been found to predict improvements in mental health following psychedelic use and psilocybin therapy (Watts et al., 2022).

1.3.8. Ego dissolution

Ego dissolution (i.e., experience of a compromised sense of self) was measured using the Ego Dissolution Inventory (EDI; Nour et al., 2016). The EDI is an item self-report that includes items such as "All notion of self and identity dissolved away" and "I experienced a dissolution of my 'self' or ego." Participants rate the extent to which each statement applied to their dosing experience on a visual analogue scale from 0 ("No, not more than usually") to 100 ("Yes, I experienced this completely/entirely"). The EDI has been shown to have good internal consistency and construct validity (Nour et al., 2016).

1.3.9. Mystical-type experience

The mystical-type experience was measured using the revised Mystical Experience Questionnaire (MEQ-30; MacLean et al., 2012). The MEQ-30 is a 30-item self-report measure composed of the following subscales: (1) mystical (i.e., experience of unity, noetic quality, and sacredness; 15 items; e.g., "Experience of unity with ultimate reality"); (2) positive mood (6 items; e.g., "Experience of amazement"); (3) transcendence (6 items; e.g., "Experience of timelessness"); and (4) ineffability (3 items; e.g., "Sense that the experience cannot be described adequately in words"). Participants rate the extent to which each statement applied to their dosing experience on a scale from 0 ("none/not at all") to 5 ("extreme [more than any other time in my life]"). The MEQ-30 has been shown to have good psychometric properties, including good internal consistency and construct validity (Barrett et al., 2015; MacLean et al., 2012).

1.3.10. Emotional breakthrough

Emotional breakthrough (i.e., an experience of emotional release) was measured using the Emotional Breakthrough Inventory (EBI; Roseman et al., 2019). The EBI is a 6-item self-report measure with items including "I was able to get a sense of closure on an emotional problem" and "I achieved an emotional release followed by a sense of relief." Participants rate each statement with regard to their dosing experience on a scale from 0 ("No, not more than usually") to 100 ("Yes, entirely or completely"). The EBI has been shown have good internal consistency, as well as discriminant and predictive validity (Roseman et al., 2019).

1.3.11. Psychological insight

Psychological insight was measured using the Psychological Insight Questionnaire (PIQ; Peill et al., 2022). The PIQ is a 6-item measure of perceived psychological insights following a psychedelic experience that includes items such as "I have had important new insights about how I would like to change aspects of myself or my lifestyle." Participants rate the extent to which they have changed since pre-treatment on a visual analogue scale from 0 ("No more than at baseline") to 100 ("Much more than at baseline"). The PIS has good internal consistency and predictive validity (Peill et al., 2022).

1.4. Data analysis

1.4.1. Preliminary analyses

All variables were examined to determine whether they were normally distributed through analysis of histograms, box plots, and Q-Q plots, as well as the Shapiro-Wilk and Kolmogorov-Smirnov tests. Correlation coefficients were analyzed for all variables at each time point. For variables that were non-normally distributed Spearman's rho was calculated. Pearson correlation coefficients were examined for all other variables.

1.4.2. Primary analyses

Structural equation modeling (SEM) was used to conduct two separate (i.e., one for each condition) two-condition within-participant mediation analyses (based on recommendations by Montoya and Hayes, 2017) for each outcome variable (i.e., well-being [WEMWBS], clinician-assessed depression severity [MADRS], self-reported depression severity [QIDS-SR-16], suicidal ideation [SIDAS], and trait anxiety [STAI-Trait]). For each analysis, the mediator (i.e., change in experiential avoidance; BEAQ) was regressed onto the intercept (*a* path). The outcome variable (i.e., well-being, clinician-assessed self-reported depression severity, suicidal ideation, or trait anxiety) was regressed onto the intercept (direct effect: *c'* path), mediator (*b* path), and grand-mean-centered average scores (across time points) of the mediator (*d path*). The indirect effect of changes in experiential avoidance on changes in each outcome were calculated by multiplying the *a* and *b* paths. Indirect effects were examined within each condition (i.e., psilocybin therapy and escitalopram). To examine differences between the strength of the indirect effects across treatment conditions, multiple groups analysis (MacKinnon et al., 2004) was implemented. For each outcome variable, the indirect effect for the escitalopram condition was subtracted from the indirect effect of the psilocybin therapy condition, and the difference in the indirect effect was tested to determine whether it was significantly different from zero. Variables were standardized according to their grand means and standard deviations. Test statistics and standard errors were calculated using bootstrapping with 5000 samples.

1.4.3. Exploratory analyses

An exploratory serial mediation model examined whether improvement in mental health outcomes occurred via (a) reduction in experiential avoidance through increases in connectedness (ΔExperiential avoidance - > ΔConnectedness - > ΔMental health outcome); and (b) increases in connectedness through reductions in experiential avoidance (ΔConnectedness - > ΔExperiential avoidance - > ΔMental health outcome). Using the same method as described above (two-condition within-participant mediation analyses), an additional mediator (i.e.,

change in connectedness; WCS) was added to the model. For each analysis, this mediator was also regressed onto the intercept (*e* path) and the outcome variable was regressed on the mediator (*f* path) and the grand-mean-centered average scores (across time points) of the mediator (*g path*). The indirect effect of changes in connectedness on changes in each outcome were calculated by multiplying the *e* and *f* paths. Changes in connectedness were then regressed onto changes in experiential avoidance (or vice versa; *h* path) and the grand-mean-centered average scores (across time points) of experiential avoidance (or vice versa; *i* path). The pathway of changes in experiential avoidance on changes in each outcome through changes in connectedness (ΔExperiential avoidance - > ΔConnectedness - > ΔMental health outcome) were calculated by multiplying the *a, h*, and *f*, and paths. The pathway of changes in connectedness on changes in each outcome through changes in experiential avoidance (ΔConnectedness - > ΔExperiential avoidance - > ΔMental health outcome) were calculated by multiplying the *e, h*, and *b* paths. Similar to above, multiple groups analysis was implemented to compare the strength of each serial mediation across treatment conditions.

Within each condition, exploratory analyses also examined the association (Spearman's rho due to non-normality) between changes in experiential avoidance (post-treatment – pre-treatment) and experiences of: (a) ego dissolution; (b) mystical-type experience; (c) emotional breakthrough; and (d) psychological insight. In line with past research (e.g., Murphy et al., 2022), the maximum score for the measures of acute psilocybin experience (i.e., ego dissolution, mystical-type experience, and emotional breakthrough) were used for these analyses. The alpha was set at $p < .05$, two-tailed.

2. Results

2.1. Descriptive statistics and preliminary analyses

A total of 59 participants enrolled in the study. Thirty participants were randomly assigned to the psilocybin therapy condition and 29 were randomly assigned to the escitalopram condition. All participants attended their first psilocybin dosing session. Two participants in the psilocybin therapy condition and one participant in the escitalopram condition were unable to attend their second dosing session and subsequent in-person visits due to COVID-19–related restrictions. One participant in the psilocybin therapy condition stopped taking their daily capsules after guessing their content and two participants in the escitalopram condition stopped taking their daily capsules due to experiencing adverse events. One participant in the escitalopram condition correctly guessed that their capsules contained escitalopram and reduced their daily dose from 20 mg to 10 mg. The final sample (Mean age = 41.22; *SD* = 10.91) was predominantly male (66.1 %), white (88.1 %), and had a university level of education (93.2 %). The duration of participants' MDD ranged from 2 to 46 years (mean duration = 18.66). For participant demographics and clinical characteristics by condition, see Table 1. For correlation coefficients by condition, see Supplementary Material (eTable 1).

2.2. Primary analysis

2.2.1. Psilocybin therapy condition

For each of the indirect effect analyses within the psilocybin therapy condition, there was a significant reduction in experiential avoidance over time (see *a* paths). Controlling for changes in experiential avoidance, there were significant increases in well-being and decreases in clinician-assessed depression severity, self-reported depression severity, and trait anxiety, but not suicidal ideation (see *c'* paths). Reductions in experiential avoidance predicted increases in well-being and decreases in clinician-assessed depression severity, self-reported depression severity, suicidal ideation, and trait anxiety (see *b* paths). Grand mean centered experiential avoidance did not predict changes in well-being, clinician-assessed depression severity, self-reported depression severity, suicidal ideation, or trait anxiety (see *d* paths). Consistent with our hypotheses, increases in well-being ($B = 4.51$, $SE = 1.98$, $p_{boot} < 0.001$) and decreases in clinician-assessed depression severity ($B = -3.32$, $SE = 1.49$, $p_{boot} = 0.010$), self-reported

Table 1
Sample demographics and clinical characteristics.

	Escitalopram $n = 29$	Psilocybin Therapy $n = 30$
Age-Mean (SD; range)	39.1 (11.7; 22–60)	43.3 (9.7; 21–64)
	n (%)	*n (%)*
Gender-Female	9 (31.0)	11 (37.0)
White	24 (82.8)	28 (93.3)
University Level of Education-Yes	23 (79.2)	22 (73.3)
Employment Status		
Employed (Non-student)	21 (72.4)	20 (66.7)
Retired	0 (0.0)	1 (3.3)
Student (Unemployed)	1 (3.4)	2 (6.7)
Student and Employed	2 (6.9)	0 (0.0)
Unemployed	5 (17.2)	7 (23.3)
Previous Psilocybin Use-Yes	8 (27.6)	8 (26.7)
Discontinuation of Psychiatric Medication for Trial	12 (40.0)	12 (41.4)
Discontinuation of SSRIs/SNRIs for Trial	11 (36.7)	9 (31.0)
Previous Psychotherapy-Yes	26 (89.7)	28 (93.3)
	Mean (SD; range)	Mean (SD; range)
# of Lifetime Psychiatric Medications Used	1.8 (1.5; 0–5)	2.2 (1.6; 0–6)
Duration of MDD in Years	15.1 (11.0; 2–46)	22.1(10.7; 3–44)
Baseline Depression Severity		
MADRS	26.86 (5.26; 16–37)	27.93 (4.03; 21–37)
Mild	2 (6.9 %)	0 (0.0 %)
Moderate	25 (86.2 %)	28 (93.3 %)
Severe	2 (6.9 %)	2 (6.7 %)
QIDS-SR-16	16.45 (4.13; 6–22)	14.53 (3.88; 7–23)
Mild	2 (6.9 %)	5 (16.7 %)
Moderate	8 (27.6 %)	12 (40.0 %)
Severe	14 (48.3 %)	11 (36.7 %)
Very severe	5 (17.2 %)	2 (6.7 %)

Note. MADRS = Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979). MDD = Major depressive disorder. QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report (Rush et al., 2003). SNRIs = Serotonin and norepinephrine reuptake inhibitors.

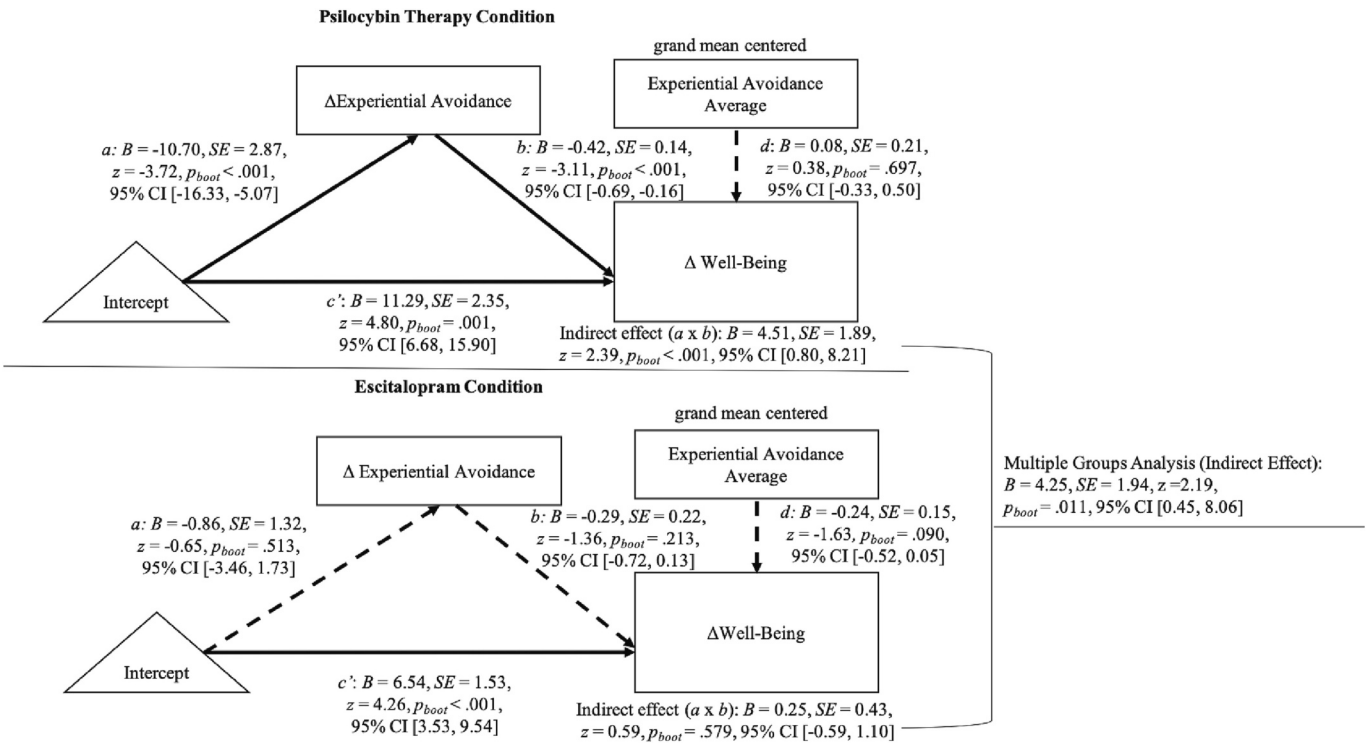

Fig. 1. Increases in Well-Being via Reductions in Experiential Avoidance (Psilocybin Therapy Condition vs. Escitalopram Condition)
Note. Solid arrows represent significant effects ($p < .05$) and dashed lines represent non-significant effects ($p > .05$).

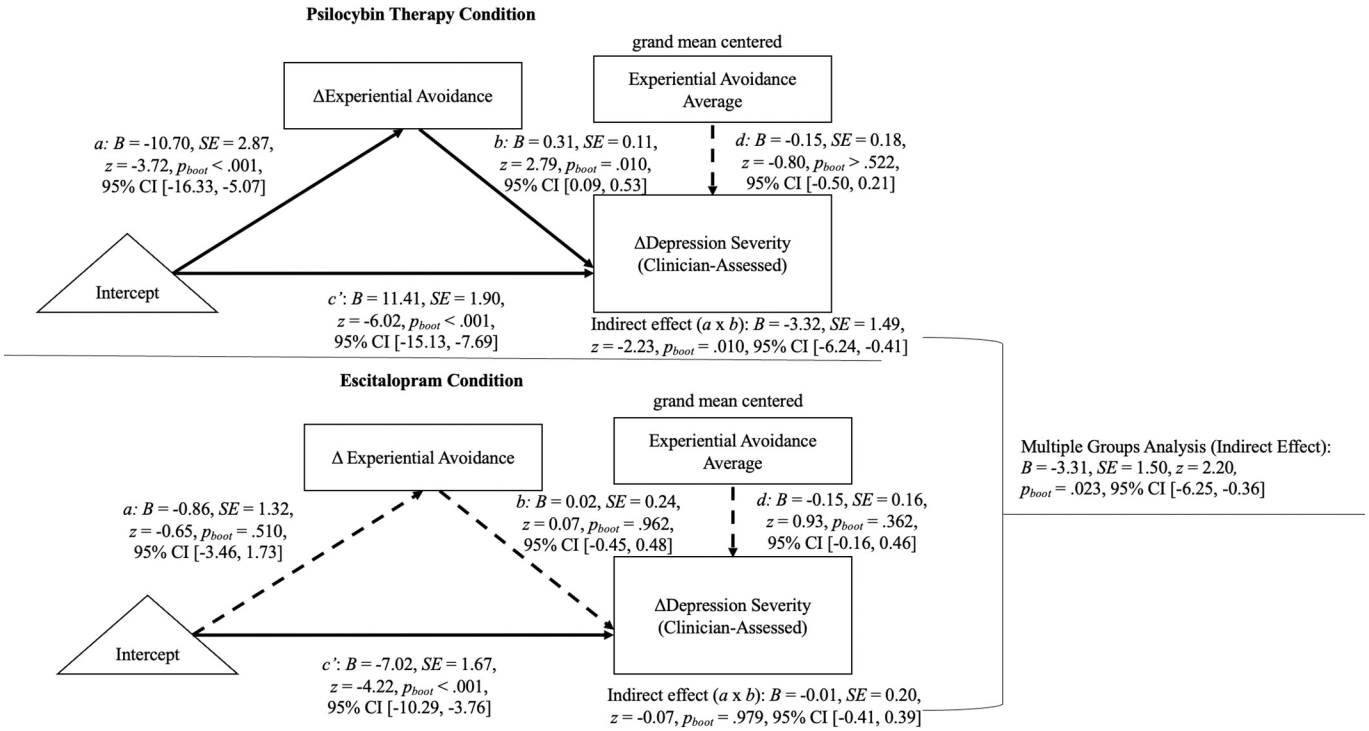

Fig. 2. Decreases in Clinician-Assessed Depression Severity via Reductions in Experiential Avoidance (Psilocybin Therapy Condition vs. Escitalopram Condition)
Note. Solid arrows represent significant effects ($p < .05$) and dashed lines represent non-significant effects ($p > .05$).

depression severity ($B = -1.82$, $SE = 0.94$, $p_{boot} = 0.015$), suicidal ideation ($B = -1.88$, $SE = 0.94$, $p_{boot} = 0.010$), and trait anxiety ($B = -5.21$, $SE = 2.14$, $p_{boot} = 0.003$) via reductions in experiential avoidance were all significant (see *a* x *b* paths). See Figs. 1-5.

2.2.2. Escitalopram condition

For each of the indirect effect analyses within the escitalopram condition, there was not a significant reduction in experiential avoidance over time (see *a* paths). Controlling for changes in experiential avoidance, there were significant increases in well-being, and decreases

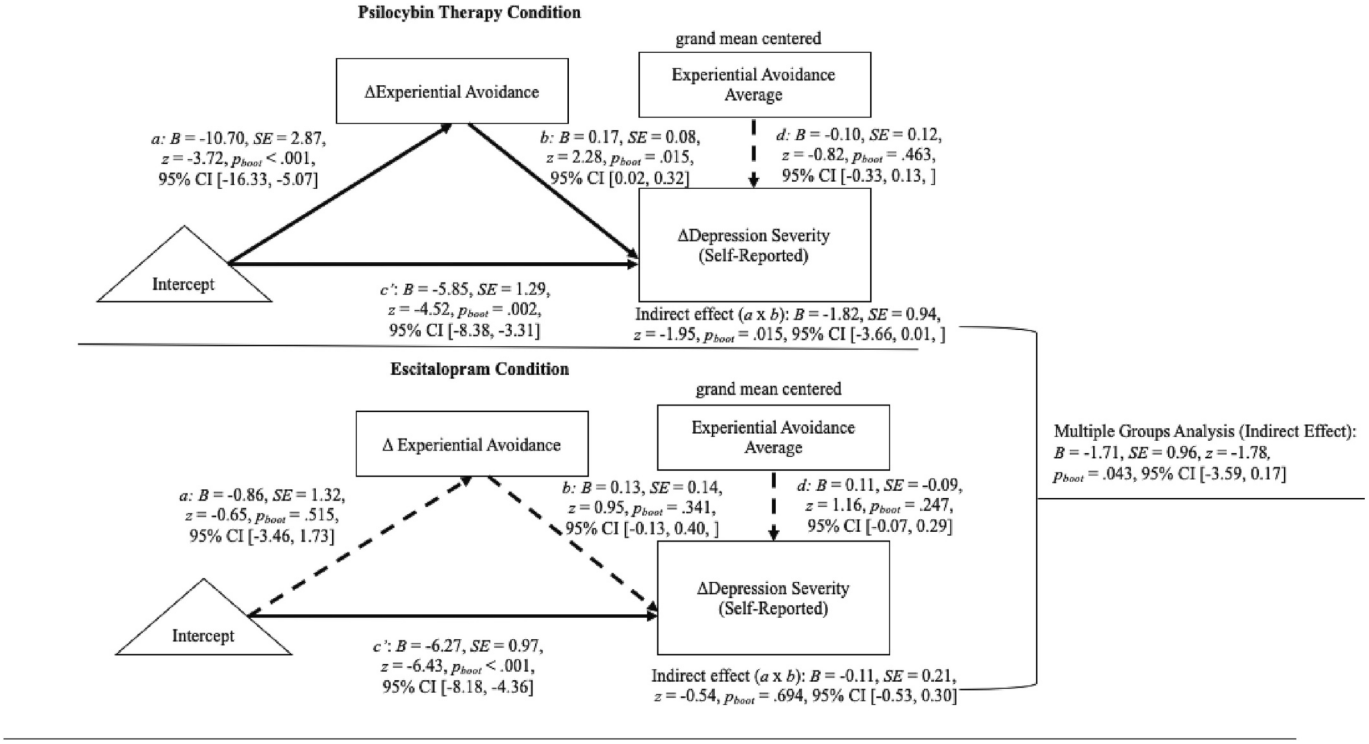

Fig. 3. Decreases in Self-Reported Depression Severity via Reductions in Experiential Avoidance (Psilocybin Therapy Condition vs. Escitalopram Condition)
Note. Solid arrows represent significant effects ($p < .05$) and dashed lines represent non-significant effects ($p > .05$).

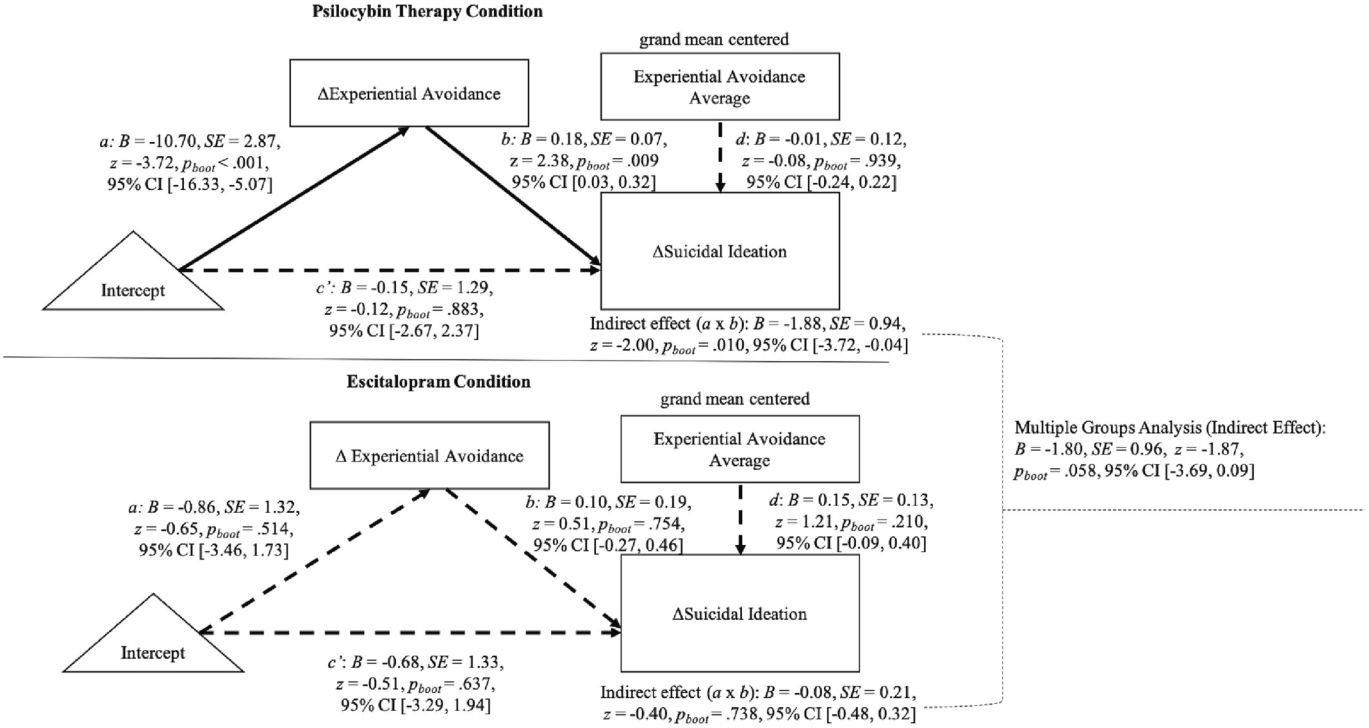

Fig. 4. Decreases in Suicidal Ideation via Reductions in Experiential Avoidance (Psilocybin Therapy Condition vs. Escitalopram Condition)
Note. Solid arrows represent significant effects ($p < .05$) and dashed lines represent non-significant effects ($p > .05$).

in clinician-assessed depression severity, self-reported depression severity, and trait anxiety, but not suicidal ideation (see *c'* paths). Changes in experiential avoidance did not significantly predict changes in well-being, clinician-assessed depression severity, self-reported depression severity, suicidal ideation, or trait anxiety (see *b* paths). Grand mean centered experiential avoidance did not significantly predict changes in well-being, clinician-assessed depression severity, self-reported depression severity (*c'* paths), suicidal ideation, and trait anxiety (see *d* paths). The indirect effect of increases in well-being ($B = 0.25$, $SE = 0.43$, $p_{boot} = 0.579$) and decreases in clinician-assessed

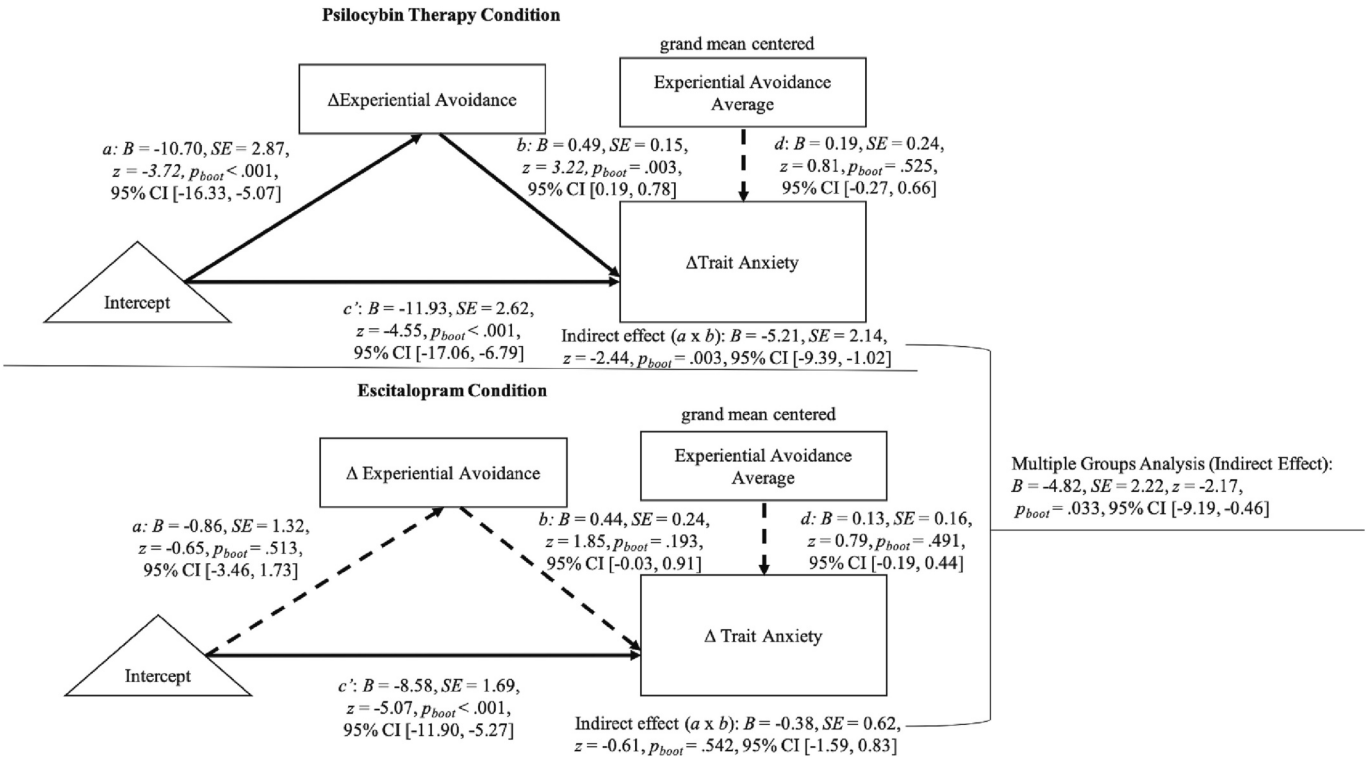

Fig. 5. Decreases in Trait Anxiety via Reductions in Experiential Avoidance (Psilocybin Therapy Condition vs. Escitalopram Condition)
Note. Solid arrows represent significant effects ($p < .05$) and dashed lines represent non-significant effects ($p > .05$).

depression severity ($B = -0.01$, $SE = 0.20$, $p_{boot} = 0.979$), self-reported depression severity ($B = -0.11$, $SE = 0.21$, $p_{boot} = 0.694$), suicidal ideation ($B = -0.08$, $SE = 0.21$, $p_{boot} = 0.738$), and trait anxiety ($B = -0.38$, $SE = 0.62$, $p_{boot} = 0.542$) via reductions in experiential avoidance were all not significant (see *a* x *b* paths). See Figs. 1-5.

2.2.3. Psilocybin therapy condition vs. escitalopram condition (multiple groups analysis)

Consistent with our hypotheses, multiple groups analysis indicated the indirect effect of increases in well-being ($B = 4.25$, $SE = 1.94$, $p_{boot} = 0.011$), decreases in clinician-assessed depression severity ($B = -3.31$, $SE = 1.50$, $p_{boot} = 0.023$), self-reported depression severity ($B = -1.71$, $SE = 0.96$, $p_{boot} = 0.043$), and trait anxiety ($B = -4.82$, $SE = 2.22$, $p_{boot} = 0.033$) via reductions in experiential avoidance was significantly greater within the psilocybin therapy condition (vs. escitalopram condition). In contrast with our hypothesis, multiple groups analysis indicated the indirect effect of decreases in suicidal ideation ($B = -1.80$, $SE = 0.96$, $p_{boot} = 0.058$) via reductions in experiential avoidance was not significantly greater within the psilocybin therapy condition (vs. escitalopram condition). See Figs. 1-5.

2.3. Exploratory analyses

2.3.1. Serial mediation of experiential avoidance, connectedness, and mental health outcomes

2.3.1.1. Psilocybin condition. Within the psilocybin therapy condition, serial mediation of improvements in mental health via reductions in experiential avoidance through increases in connectedness (ΔExperiential avoidance - > ΔConnectedness - > ΔMental health outcome) was significant for increases in well-being ($B = 1.84$, $SE = 1.14$, $p_{boot} = 0.040$) and decreases in clinician-assessed depression severity ($B = -2.20$, $SE = 1.21$, $p_{boot} = 0.028$), self-reported depression severity ($B = -1.33$, $SE = 0.74$, $p_{boot} = 0.008$), and trait anxiety ($B = 2.09$, $SE = 1.31$, $p_{boot} = 0.040$), but not suicidal ideation ($B = -0.03$, $SE = 0.45$, $p_{boot} = 0.932$). Serial mediation of improvements in mental health via increases in connectedness through reductions in experiential avoidance (ΔConnectedness - > ΔExperiential avoidance - > ΔMental health outcome) was not statistically significant for any of the mental health outcomes (well-being $B = 3.50$, $SE = 2.22$, $p_{boot} = 0.073$; clinician-assessed depression severity $B = -1.48$, $SE = 1.43$, $p_{boot} = 0.212$; self-reported depression severity $B = -0.69$, $SE = 0.90$, $p_{boot} = 0.329$; trait anxiety $B = 4.24$, $SE = 2.62$, $p_{boot} = 0.052$; suicidal ideation $B = -2.35$, $SE = 1.48$, $p_{boot} = 0.060$. See Supplementary Material (eTables 2–11).

2.3.1.2. Escitalopram condition. Within the escitalopram condition, serial mediation of improvements in mental health via reductions in experiential avoidance through increases in connectedness (ΔExperiential avoidance - > ΔConnectedness - > ΔMental health outcome) was not statistically significant for any of the mental health outcomes (well-being $B = 0.21$, $SE = 0.35$, $p_{boot} = 0.539$; clinician-assessed depression severity $B = -0.09$, $SE = 0.20$, $p_{boot} = 0.762$; self-reported depression severity $B = 0.03$, $SE = 0.08$, $p_{boot} = 0.924$; trait anxiety $B = -0.01$, $SE = 0.13$, $p_{boot} = 0.857$; suicidal ideation $B = 0.15$, $SE = 0.26$, $p_{boot} = 0.582$). Similarly, serial mediation of improvements in mental health via increases in connectedness through reductions in experiential avoidance (ΔConnectedness - > ΔExperiential avoidance - > ΔMental health outcome) was not statistically significant for any of the mental health outcomes (well-being $B = -0.15$, $SE = 0.34$, $p_{boot} = 0.619$; clinician-assessed depression severity $B = 0.33$, $SE = 0.44$, $p_{boot} = 0.520$; self-reported depression severity $B = 0.08$, $SE = 0.21$, $p_{boot} = 0.710$; trait anxiety $B = 0.24$, $SE = 0.41$, $p_{boot} = 0.694$; suicidal ideation $B = -0.04$, $SE = 0.30$, $p_{boot} = 0.926$). See Supplementary Material (eTables 2–11).

2.3.1.3. Psilocybin therapy condition vs. escitalopram condition (multiple groups analysis). Multiple groups analysis indicated the serial mediation via reductions in experiential avoidance through increases in

connectedness (ΔExperiential avoidance - > ΔConnectedness - > ΔMental health outcome) was significantly greater within the psilocybin therapy condition (vs. escitalopram condition) for self-reported depression severity ($B = -1.35$, $SE = 0.75$, $p_{boot} = 0.015$) and trait anxiety ($B = 2.10$, $SE = 1.32$, $p_{boot} = 0.045$), but not for well-being ($B = 1.62$, $SE = 1.19$, $p_{boot} = 0.123$), clinician-assessed depression severity ($B = -2.11$, $SE = 1.23$, $p_{boot} = 0.067$), or suicidal ideation ($B = -0.18$, $SE = 0.52$, $p_{boot} = 0.738$). For the inverse model (ΔConnectedness - > ΔExperiential avoidance - > ΔMental health outcome) multiple groups analysis indicated that the effect was not significantly greater within the psilocybin therapy condition (vs. escitalopram condition) for any of the mental health outcomes (well-being $B = 3.65$, $SE = 2.24$, $p_{boot} = 0.069$; clinician-assessed depression severity $B = -1.81$, $SE = 1.49$, $p_{boot} = 0.160$; self-reported depression severity $B = -0.76$, $SE = 0.93$, $p_{boot} = 0.296$; trait anxiety $B = 4.01$, $SE = 2.65$, $p_{boot} = 0.100$; suicidal ideation $B = -2.31$, $SE = 1.51$, $p_{boot} = 0.082$). See Supplementary Material (eTables 2–11).

2.3.2. Predictors of reductions in experiential avoidance

Within the psilocybin condition, reductions in experiential avoidance were positively associated with experiences of ego dissolution ($r_s = -0.48$, $p = .007$) and psychological insight ($r_s = -0.38$, $p = .037$). Reductions in experiential avoidance were not significantly associated with experiences of mystical-type experience ($r_s = -0.30$, $p = .107$) or emotional breakthrough ($r_s = 0.10$, $p = .592$). Within the escitalopram condition, changes in experiential avoidance were not significantly associated with experiences of ego dissolution ($r_s = -0.01$, $p = .942$), mystical-type experience ($r_s = 0.03$, $p = .890$), emotional breakthrough ($r_s = 0.18$, $p = .360$), or psychological insight ($r_s = 0.06$, $p = .775$).

3. Discussion

Psilocybin therapy shows promise as an intervention for a range of mental health concerns, including depression severity (Goldberg et al., 2020), anxiety (Weston et al., 2020), and suicidal ideation (Zeifman et al., 2022a). Qualitative (Agin-Liebes et al., 2021; Watts et al., 2017) and survey-based (e.g., Davis et al., 2020a) research suggest that psilocybin therapy may lead to positive therapeutic outcomes by targeting experiential avoidance, a key transdiagnostic factor in mental health (Bullis et al., 2019). However, to-date, no psilocybin therapy trials have quantitatively examined the relationship between: (a) reductions in experiential avoidance and therapeutic outcomes; (b) reductions in experiential avoidance and increases in connectedness in predicting therapeutic outcomes; or (c) psilocybin experiences and reductions in experiential avoidance. We found that among individuals with MDD, improvements in mental health occurred via reductions in experiential avoidance following psilocybin therapy. These results were consistent across all examined indicators of mental health, including well-being, depression severity (self-report and clinician-assessed), suicidal ideation, and trait anxiety. Exploratory serial mediation analyses indicated that the effects of experiential avoidance on improved mental health outcomes (except for suicidal ideation) occurred through increases in connectedness. Moreover, the role of experiential avoidance and connectedness in mediating mental health improvement, was not shared by a gold-standard SSRI antidepressant (escitalopram). Within psilocybin therapy, experiences of ego dissolution and psychological insight predicted reductions in experiential avoidance.

Our findings are in line with previous research linking reductions in experiential avoidance with improvements in depression severity, anxiety, and suicidal ideation following psychedelic use within non-clinical convenience samples (e.g., Davis et al., 2020a). The present findings are also consistent with qualitative research from several previous psilocybin therapy trials (Agin-Liebes et al., 2021; Belser et al., 2017; Watts et al., 2017; Crowe et al., 2023), which has highlighted the importance of shifting from avoidance to acceptance and from disconnectedness to connectedness as key themes that participants highlight as contributing to their improvement following treatment. Our findings are also consistent with empirical evidence and theoretical modeling that highlights improved experiential acceptance as a transdiagnostically relevant therapeutic mechanism in mental health care (Sloan et al., 2017). Overall, these results suggest that psilocybin therapy may lead to improvements in mental health by allowing individuals to approach and be open to (rather than avoid) their emotions (and in turn, shifting toward a sense of connectedness), implying that this treatment modality is effective at targeting a putative common denominator of mental suffering (i.e., experiential avoidance; Carhart-Harris and Friston, 2019; Kočárová et al., 2021). Accordingly, psilocybin therapy may be efficacious for several clinical presentations characterized by heightened experiential avoidance, including anxiety and depression in the context of a life-threatening illness (Griffiths et al., 2016; Ross et al., 2016) and various addictions (e.g., Bogenschutz et al., 2022), in part, via its positive action on experiential avoidance.

In contrast with the significant indirect effects within the psilocybin therapy condition, change in experiential avoidance was not a significant component of the improvements in mental health outcomes seen within the escitalopram condition. Moreover, the indirect effects of reductions in experiential avoidance on improvements in several mental health outcomes were significantly larger in the psilocybin therapy condition. These results were generally consistent across both positive (i.e., increases in well-being) and negative (i.e., decreases in depression severity and trait anxiety) measures of mental health (but were not observed for reductions in suicidal ideation). Additionally, for the serial mediation analyses, the improvements in self-reported depression severity and trait anxiety via reductions in experiential avoidance through increases in connectedness were also significantly larger in the psilocybin therapy condition. These findings are in line with previous suggestions that psilocybin and SSRIs lead to changes via two somewhat distinct serotonergic neural pathways (Carhart-Harris and Nutt, 2017). More specifically, Carhart-Harris and Nutt (2017) suggest that SSRIs facilitate improvements in mental health by increasing passive coping (i.e., increasing tolerance of but not actively dealing with a source of psychological distress) via increased post-synaptic (inhibitory) 5-HT_{1A} receptor signalling (densely expressed in central stress circuitry) through elevated synaptic 5-HT, while psilocybin therapy increases active coping (i.e., actively dealing with psychological distress, or its causes, by changing one's relationship to it) via excitatory 5-HT_{2A} receptor signalling (densely expressed in high-level association cortices).

Previous research suggests that psilocybin therapy may actually increase emotional responsiveness in clinical samples (e.g., Roseman et al., 2018), while a broad range of research suggests that SSRIs may down-regulate emotional responsiveness and, in some cases, cause emotional numbing or blunting (e.g., Goodwin et al., 2017; Kajanoja et al., 2018). Similarly, qualitative research conducted in the context of a psilocybin therapy trial found that individuals with treatment-resistant depression experienced antidepressants as medications that suppressed and blunted their emotions and that psilocybin therapy helped to increase their emotional responsiveness and decrease their emotional avoidance (Watts et al., 2017). Granted, this sample may be biased by patient's therapeutic history (i.e., failing to respond to SSRIs or other treatments); however, its findings, combined with others (e.g., Zeifman et al., 2020) and the present study's, might also suggest that psilocybin therapy is especially effective at remediating suffering by targeting experiential avoidance (a casual or perpetuating factor in psychopathology; Bullis et al., 2019).

Interestingly, the multiple groups analysis indicated that the indirect effect of psilocybin therapy on suicidal ideation via reductions in experiential avoidance was not significantly greater than the indirect effect within the escitalopram condition. This null finding may be attributable to several causes. First, it may be that the indirect effect of reductions in experiential avoidance on changes in suicidal ideation within psilocybin therapy is not an exclusive attribute (relative to escitalopram). Alternatively, the null finding may be attributable to the

relatively small sample size, fairly large standard deviations relative to the means, and the suicidal ideation data being fairly non-normally distributed. Additionally, this null result may be due to there being limited room for decreases in suicidal ideation within the present study, due to the relatively low levels of baseline suicidal ideation (i.e., a floor effect). Further research, conducted in larger samples and specifically recruited based on the presence of elevated levels of suicidal ideation (e.g., see clinical trials.gov, NCT05220410), will be necessary for exploring these possibilities.

We observed significant associations between reductions in experiential avoidance and experiences of ego dissolution and psychological insight. The latter finding is in line with previous retrospective cross-sectional research, which had found a link between experiences of psychological insight and reductions in experiential avoidance (e.g., Davis et al., 2020a, 2021b) and between experiences of ego dissolution and improvement in mental health (Kiraga et al., 2022). We did not observe significant associations between reductions in experiential avoidance and mystical-type experiences and emotional breakthrough. This is somewhat in contrast to previous retrospective research on experiential avoidance (e.g., Davis et al., 2020a) and clinical research on mental health outcomes more broadly (e.g., Murphy et al., 2022; Peill et al., 2022; and for a review, see Kangaslampi, 2023), but is in line with some recent clinical trials that have failed to find a significant link between mystical-type experiences and psilocybin therapy outcomes (Gukasyan et al., 2022; Sloshower et al., 2023). Additional research within larger samples will be necessary to more fully elucidate the elements of the psilocybin experience (including acute experiences of avoidance and acceptance; see Wolff et al., 2022) that contribute to reductions in experiential avoidance within psilocybin therapy.

3.1. Clinical implications

The present findings have several potentially important implications for psilocybin therapy. Extant research suggests that the context in which psilocybin is administered plays an important role in shaping its potential therapeutic effects (Carhart-Harris et al., 2018b; Golden et al., 2022). Accordingly, the therapeutic package that is provided alongside administration of psilocybin likely plays an important role in the extent to which psilocybin is helpful and the duration that such effects are sustained. The results of the present study suggest that the extent to which shifting from experiential avoidance to experiential openness (and from disconnectedness to connectedness) is emphasized within psilocybin therapy may be important components of *why* it is effective. They also suggest that there may be an important sequential relationship between decreasing experiential avoidance and increasing connectedness as mechanisms of change within psilocybin therapy. There is therefore reason to think that integrating psilocybin therapy with first-line interventions that specifically target experiential avoidance and connectedness may have positive synergistic effects that optimize treatment outcomes (e.g., see Sloshower et al., 2023, which combined psilocybin with elements of acceptance and commitment therapy that focus on reducing experiential avoidance and increasing valued action). Such efforts may also help to accelerate the psychotherapeutic process and may, thereby, increase its cost-effectiveness. Additionally, these results provide support for the importance of specific elements of the psilocybin experience (i.e., ego dissolution and psychological insight). The present findings also suggest that psilocybin therapy may show promise as a treatment for additional mental health presentations characterized by heightened experiential avoidance, including anorexia nervosa (Spriggs et al., 2021), posttraumatic stress disorder (Averill and Abdallah, 2022), obsessive-compulsive disorder (Angelakis and Pseftogianni, 2021; Moreno et al., 2006), and alcohol use disorder (Bogenschutz et al., 2022; Luoma et al., 2020).

3.2. Limitations and future directions

The present study included a number of important limitations. The study relied upon self-reported experiential avoidance at pre and post-treatment, which limits the extent to which the data can be used to definitively determine that changes in experiential avoidance occurred temporally prior to improvement in mental health outcomes and were therefore causally linked. Therefore, additional research that utilizes alternative methods to assess experiential avoidance, including observer-based coding (e.g., Experiencing Scale [Klein et al., 1969]), ecological momentary assessment, biological markers (e.g., physiological and neurobiological indicators of emotional response and avoidance), and measurement of acute and sub-acute experiential avoidance (Wolff et al., 2022) remain necessary. The study also included a relatively small sample size for a head-to-head trial and a fairly non-diverse sample. Therefore, research with larger and more diverse samples remains necessary for confirming the generalizability of the present findings (Thrul and Garcia-Romeu, 2021), as well as for testing more complex models (e.g., see Kettner et al., 2021) that include additional mediating (e.g., cognitive flexibility, therapeutic alliance; Doss et al., 2021; Murphy et al., 2022) and moderating (e.g., ethnicity; Jones and Nock, 2022) variables. Due to the present study's limited sample size, we also suggest particular caution when interpreting the serial mediation findings. Despite efforts to minimize expectancy effects, blindness to condition remains a concern across psilocybin therapy trials (Muthukumaraswamy et al., 2021). Accordingly, it will be important for future research to carefully consider how it can demonstrate direct treatment effects over and above those that carry a placebo response. For example, this might be done by utilising neuroimaging to examine treatment-specific changes in brain function, and the use of active placebos or control drugs, with psychoactive effects that can create uncertainty about treatment allocation (e.g., tetrahydrocannabinol [THC] or ketamine). Measuring expectancy effects, suggestibility and various aspects of blinding, will also be important (Szigeti et al., 2022). Dose-response designs (Goodwin et al., 2022), pragmatic or adaptive trial designs (Carhart-Harris et al., 2022), and idiographic approaches (Zeifman et al., 2022b, 2022c) may also be helpful for customizing treatment parameters to achieve optimal treatment outcomes. Finally, the present study used only a single clinical sample, defined principally by an MDD diagnosis. Further research that examines the role of experiential avoidance within psilocybin therapy across additional mental health concerns remains necessary.

In sum, among individuals with MDD, following psilocybin therapy, improvements across a range of mental health outcomes (i.e., well-being, depression severity, suicidal ideation, and trait anxiety) occurred via reductions in experiential avoidance. Furthermore, the indirect effect of changes in experiential avoidance were not significant within the escitalopram condition and were generally significantly larger within the psilocybin therapy condition (vs. escitalopram condition). Exploratory analyses indicated that the effect of experiential avoidance on several mental health outcomes was serially mediated through increases in connectedness and that experiences of ego dissolution and psychological insight predicted reductions in experiential avoidance. These results provide support for the role of experiential avoidance as a putative transdiagnostic mechanism underlying the positive mental health effects of psilocybin therapy, as well as the importance of connectedness and elements of the psilocybin experience within psilocybin therapy. These findings may help to guide future research and treatment providers in efforts to optimize and tailor psilocybin therapy.

CRediT authorship contribution statement

RCH contributed to the design of the study. All authors contributed toward the development and conceptualization of the present manuscript. RJZ conducted the analyses and wrote the first draft of

manuscript. All authors contributed to editing the manuscript and reviewed the manuscript in its final form.

Funding

RJZ received funding from the Canadian Institutes of Health Research (grant number: 201610GSD-385560-272687). The present clinical trial was funded by the Alexander Mosley Charitable Trust and Imperial College London's Centre for Psychedelic Research.

Declaration of competing interest

RJZ is a postdoctoral fellows in the NYU Langone Psychedelic Medicine Research Training program funded by MindMed. ACW has served as a consultant for MAPS Public Benefit Corporation. RCH is a scientific advisor to Usona Institute, Synthesis Institute, Mydecine, Maya Health, Osmind, Entheos Labs, Beckley Psychtech, TRYP therapeutics, Journey Collab and Journey Space. CMM reports no conflicts of interest.

Acknowledgements

We thank the study participants, coordinators, and therapists for their contribution to this research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.04.105.

References

Agin-Liebes, G.I., Malone, T., Yalch, M.M., Mennenga, S.E., Ponté, K.L., Guss, J., Bossis, A.P., Grigsby, J., Fischer, S., Ross, S., 2020. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. J. Psychopharmacol. 34 (2), 155–166. https://doi.org/10.1177/0269881119897615.

Agin-Liebes, G., Ekman, E., Anderson, B., Malloy, M., Haas, A., Woolley, J., 2021. Participant reports of mindfulness, posttraumatic growth, and social connectedness in psilocybin-assisted group therapy: an interpretive phenomenological analysis. J. Humanist. Psychol. https://doi.org/10.1177/00221678211022949.

Agin-Liebes, G., Zeifman, R.J., Luoma, J.B., Garland, E.L., Campbell, W.K., Weiss, B., 2022. Prospective examination of the therapeutic role of psychological flexibility and cognitive reappraisal in the ceremonial use of ayahuasca. J. Psychopharmacol. 36 (3), 295–308. https://doi.org/10.1177/02698811221080165.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. American Psychiatric Association.

Angelakis, I., Pseftogianni, F., 2021. Association between obsessive-compulsive and related disorders and experiential avoidance: a systematic review and meta-analysis. J. Psychiatr. Res. 138, 228–239. https://doi.org/10.1016/j.jpsychires.2021.03.062.

Averill, L.A., Abdallah, C.G., 2022. Investigational drugs for assisting psychotherapy for posttraumatic stress disorder (PTSD): emerging approaches and shifting paradigms in the era of psychedelic medicine. Expert Opin. Investigatig. Drugs 31 (2), 133–147. https://doi.org/10.1080/13543784.2022.2035358.

Barrett, F.S., Johnson, M.W., Griffiths, R.R., 2015. Validation of the revised mystical experience questionnaire in experimental sessions with psilocybin. J. Psychopharmacol. 29 (11), 1182–1190. https://doi.org/10.1177/0269881115609019.

Belser, A.B., Agin-Liebes, G., Swift, T.C., Terrana, S., Devenot, N., Friedman, H.L., Guss, J., Bossis, A., Ross, S., 2017. Patient experiences of psilocybin-assisted psychotherapy: an interpretative phenomenological analysis. J. Humanist. Psychol. 57 (4), 354–388. https://doi.org/10.1177/0022167817706884.

Bogenschutz, M.P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A.A., Laska, E., Worth, L., 2022. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. JAMA Psychiatry 79 (10), 953–962.

Bond, F.W., Hayes, S.C., Baer, R.A., Carpenter, K.M., Guenole, N., Orcutt, H.K., Waltz, T., Zettle, R.D., 2011. Preliminary psychometric properties of the acceptance and action Questionnaire–II: a revised measure of psychological inflexibility and experiential avoidance. Behav. Ther. 42 (4), 676–688. https://doi.org/10.1016/j.beth.2011.03.007.

Bullis, J.R., Boettcher, H., Sauer-Zavala, S., Farchione, T.J., Barlow, D.H., 2019. What is an emotional disorder? A transdiagnostic mechanistic definition with implications for assessment, treatment, and prevention. Clin. Psychol. 26 (2), e12278 https://doi.org/10.1111/cpsp.12278.

Carhart-Harris, R.L., Friston, K.J., 2019. REBUS and the anarchic brain: toward a unified model of the brain action of psychedelics. Pharmacol. Rev. 71 (3), 316–344. https://doi.org/10.1124/pr.118.017160.

Carhart-Harris, R.L., Nutt, D.J., 2017. Serotonin and brain function: a tale of two receptors. J. Psychopharmacol. 31 (9), 1091–1120. https://doi.org/10.1177/0269881117725915.

Carhart-Harris, R.L., Bolstridge, M., Day, C.M.J., Rucker, J., Watts, R., Erritzoe, D.E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J.A., Forbes, B., Feilding, A., Taylor, D., Curran, H.V., Nutt, D.J., 2018a. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology 235 (2), 399–408. https://doi.org/10.1007/s00213-017-4771-x.

Carhart-Harris, R.L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., Kaelen, M., 2018b. Psychedelics and the essential importance of context. J. Psychopharmacol. 32 (7), 725–731. https://doi.org/10.1177/0269881118754710.

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoie, D., Nutt, D.J., 2021. Trial of psilocybin versus escitalopram for depression. NEJM 384 (15), 1402–1411. https://doi.org/10.1056/NEJMoa2032994.

Carhart-Harris, R.L., Wagner, A.C., Agrawal, M., Kettner, H., Rosenbaum, J.F., Gazzaley, A., Nutt, D.J., Erritzoe, D., 2022. Can pragmatic research, real-world data and digital technologies aid the development of psychedelic medicine? J. Psychopharmacol. 36 (1), 6–11. https://doi.org/10.1177/02698811211008567.

Carhart-Harris, R.L., Chandaria, S., Erritzoe, D.E., Gazzaley, A., Girn, M., Kettner, H., Friston, K.J., 2023. Canalization and plasticity in psychopathology. Neuropharmacology, 109398. https://doi.org/10.1016/j.neuropharm.2022.109398.

Carmody, T.J., Rush, A.J., Bernstein, I., Warden, D., Brannan, S., Burnham, D., Woo, A., Trivedi, M.H., 2006. The Montgomery Äsberg and the Hamilton ratings of depression: a comparison of measures. Eur. Neuropsychopharmacol. 16 (8), 601–611. https://doi.org/10.1016/j.euroneuro.2006.04.008.

Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ionnidis, J.P.A., Geddes, J.R., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Focus 16 (4), 420–429. https://doi.org/10.1176/appi.focus.16407.

Close, J.B., Hajien, E.C., Watts, R., Roseman, L., Carhart-Harris, R.L., 2020. Psychedelics and psychological flexibility-results of a prospective web-survey using the acceptance in action questionnaire II. J. Contextual Behav. Sci. 16, 37–44. https://doi.org/10.1016/j.jcbs.2020.01.005.

Crowe, M., Manuel, J., Carlyle, D., Lacey, C., 2023. Experiences of psilocybin treatment for clinical conditions: a qualitative meta-synthesis. Int. J. Ment. Health Nurs. https://doi.org/10.1111/inm.13127. Advance online publication.

Davis, A.K., Barsuglia, J.P., Lancelotta, R., Grant, R.M., Renn, E., 2018. The epidemiology of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) use: benefits, consequences, patterns of use, subjective effects, and reasons for consumption. J. Psychopharmacol. 32 (7), 779–792. https://doi.org/10.1177/0269881118769063.

Davis, A.K., Averill, L.A., Sepeda, N.D., Barsuglia, J.P., Amoroso, T., 2020b. Psychedelic treatment for trauma-related psychological and cognitive impairment among US special operations forces veterans. Chronic Stress 4, 2470547020939564.

Davis, A.K., Barrett, F.S., Griffiths, R.R., 2020a. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. J. Contextual Behav. Sci. 15, 39–45. https://doi.org/10.1016/j.jcbs.2019.11.004.

Davis, A.K., Barrett, F.S., May, D.G., Cosimano, M.P., Sepeda, N.D., Johnson, M.W., Finan, P.H., Griffiths, R.R., 2021a. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiatry 78 (5), 481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285.

Davis, A.K., Barrett, F.S., So, S., Gukasyan, N., Swift, T.C., Griffiths, R.R., 2021b. Development of the psychological insight questionnaire among a sample of people who have consumed psilocybin or LSD. J. Psychopharmacol. 35 (4), 437–446. https://doi.org/10.1177/0269881120967878.

Doss, M.K., Považan, M., Rosenberg, M.D., Sepeda, N.D., Davis, A.K., Finan, P.H., Barrett, F.S., 2021. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. Transl. Psychiatry 11 (1), 574. https://doi.org/10.1038/s41398-021-01706-y.

Ellis, T.E., Rufino, K.A., 2016. Change in experiential avoidance is associated with reduced suicidal ideation over the course of psychiatric hospitalization. Arch. Suicide Res. 20 (3), 426–437. https://doi.org/10.1080/13811118.2015.1093983.

Espejo, E.P., Gorlick, A., Castriotta, N., 2017. Changes in threat-related cognitions and experiential avoidance in group-based transdiagnostic CBT for anxiety disorders. J. Anxiety Disord. 46, 65–71. https://doi.org/10.1016/j.janxdis.2016.06.006.

Eustis, E.H., Cardona, N., Nauphal, M., Sauer-Zavala, S., Rosellini, A.J., Farchione, T.J., Barlow, D.H., 2020. Experiential avoidance as a mechanism of change across cognitive-behavioral therapy in a sample of participants with heterogeneous anxiety disorders. Cognit. Ther. Res. 44, 275–286. https://doi.org/10.1007/s10608-019-10063-6.

Gámez, W., Chmielewski, M., Kotov, R., Ruggero, C., Suzuki, N., Watson, D., 2014. The brief experiential avoidance questionnaire: development and initial validation. Psychol. Assess. 26 (1), 35–45. https://doi.org/10.1037/a0034473.

Goldberg, S.B., Pace, B.T., Nicholas, C.R., Raison, C.L., Hutson, P.R., 2020. The experimental effects of psilocybin on symptoms of anxiety and depression: a meta-analysis. Psychiatry Res. 284, 112749 https://doi.org/10.1016/j.psychres.2020.112749.

Golden, T.L., Magsamen, S., Sandu, C.C., Lin, S., Roebuck, G.M., Shi, K.M., Barrett, F.S., 2022. Effects of setting on psychedelic experiences, therapies, and outcomes: a rapid scoping review of the literature. In: Barret, F.S., Preller, K.H. (Eds.), Current Topics

in Behavioral Neurosciences, volume 56. Springer. https://doi.org/10.1007/7854_2021_298.
Goodwin, G.M., Price, J., De Bodinat, C., Laredo, J., 2017. Emotional blunting with antidepressant treatments: a survey among depressed patients. J. Affect. Disord. 221, 31–35. https://doi.org/10.1016/j.jad.2017.05.048.
Goodwin, G.M., Aaronson, S.T., Alvarez, O., Arden, P.C., Baker, A., Bennett, J.C., Bird, C., Blom, R.E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B.W., Eisen, K., Feifel, D., Malievskaia, E., 2022. Single-dose psilocybin for a treatment-resistant episode of major depression. NEJM 387 (18), 1637–1648. https://doi.org/10.1056/NEJMoa2206443.
Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P., Klinedinst, M.A., 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J. Psychopharmacol. 30 (12), 1181–1197. https://doi.org/10.1177/0269881116675513.
Gukasyan, N., Davis, A.K., Barrett, F.S., Cosimano, M.P., Sepeda, N.D., Johnson, M.W., Griffiths, R.R., 2022. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: prospective 12-month follow-up. J. Psychopharmacol. 36 (2), 151–158. https://doi.org/10.1177/02698811211073759.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23 (1), 56–62. https://doi.org/10.1136/jnnp.23.1.56.
Hayes, S.C., Strosahl, K., Wilson, K.G., Bissett, R.T., Pistorello, J., Toarmino, D., Polusny, M.A., Dykstra, T.A., Batten, S.V., Bergan, J., Stewart, S.H., Zvolensky, M.J., Eifert, G.H., Bond, F.W., Forsyth, J.P., Karekla, M., McCurry, S.M., 2004. Measuring experiential avoidance: a preliminary test of a working model. Psychol. Rec. 54 (4), 553–578. https://doi.org/10.1007/BF03395492.
Jankowski, P.J., Captari, L.E., Sandage, S.J., 2021. Exploring virtue ethics in psychodynamic psychotherapy: latent changes in humility, affect regulation, symptoms and well-being. Couns. Psychother. Res. 21 (4), 983–991. https://doi.org/10.1002/capr.12389.
Johnson, M.W., Richards, W.A., Griffiths, R.R., 2008. Human hallucinogen research: guidelines for safety. J. Psychopharmacol. 22 (6), 603–620. https://doi.org/10.1177/0269881108093587.
Jones, G.M., Nock, M.K., 2022. Race and ethnicity moderate the associations between lifetime psychedelic use (MDMA and psilocybin) and psychological distress and suicidality. Sci. Rep. 12 (1), 16976. https://doi.org/10.1038/s41598-022-18645-3.
Kaelen, M., Giribaldi, B., Raine, J., Evans, L., Timmerman, C., Rodriguez, N., Roseman, L., Feilding, A., Nutt, D., Carhart-Harris, R., 2018. The hidden therapist: evidence for a central role of music in psychedelic therapy. Psychopharmacology 235 (2), 505–519. https://doi.org/10.1007/s00213-018-4886-8.
Kajanoja, J., Scheinin, N.M., Karukivi, M., Karlsson, L., Karlsson, H., 2018. Is antidepressant use associated with difficulty identifying feelings? A brief report. Exp. Clin. Psychopharmacol. 26 (1), 2–5. https://doi.org/10.1037/pha0000165.
Kangaslampi, S., 2023. Association between mystical-type experiences under psychedelics and improvements in well-being or mental health–a comprehensive review of the evidence. J. Psychedelic Stud. https://doi.org/10.1556/2054.2023.00243. Advance online publication.
Kazdin, A.E., 2007. Mediators and mechanisms of change in psychotherapy research. Annu. Rev. Clin. Psychol. 3, 1–27. https://doi.org/10.1146/annurev.clinpsy.3.022806.091432.
Kettner, H., Rosas, F.E., Timmermann, C., Kärtner, L., Carhart-Harris, R.L., Roseman, L., 2021. Psychedelic communitas: intersubjective experience during psychedelic group sessions predicts enduring changes in psychological wellbeing and social connectedness. Front. Pharmacol. 12, 623985 https://doi.org/10.3389/fphar.2021.623985.
Kiraga, M.K., Kuypers, K.P., Uthaug, M.V., Ramaekers, J.G., Mason, N.L., 2022. Decreases in state and trait anxiety post-psilocybin: a naturalistic, observational study among retreat attendees. Front. Psychiatry 13. https://doi.org/10.3389/fpsyt.2022.883869.
Klein, M.H., Mathieu, P.L., Gendlin, E.T., Kiesler, D.J., 1969. The Experiencing Scale: A Research and Training Manual. Two Volumes. Wisconsin Psychiatric Institute.
Kočárová, R., Horacek, J., Carhart-Harris, R., 2021. Does psychedelic therapy have a transdiagnostic action and prophylactic potential? Front. Psychiatry 12, 1068. https://doi.org/10.3389/fpsyt.2021.661233.
Luoma, J.B., Pierce, B., Levin, M.E., 2020. Experiential avoidance and negative affect as predictors of daily drinking. Psychol. Addict. Behav. 34 (3), 421–433. https://doi.org/10.1037/adb0000554.
MacKinnon, D.P., Lockwood, C.M., Williams, J., 2004. Confidence limits for the indirect effect: distribution of the product and resampling methods. Multivar. Behav. Res. 39 (1), 99–128. https://doi.org/10.1207/s15327906mbr3901_4.
MacLean, K.A., Leoutsakos, J.M.S., Johnson, M.W., Griffiths, R.R., 2012. Factor analysis of the mystical experience questionnaire: a study of experiences occasioned by the hallucinogen psilocybin. J. Sci. Study Relig. 51 (4), 721–737. https://doi.org/10.1111/j.1468-5906.2012.01685.x.
Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134 (4), 382–389. https://doi.org/10.1192/bjp.134.4.382.
Montoya, A.K., Hayes, A.F., 2017. Two-condition within-participant statistical mediation analysis: a path-analytic framework. Psychol. Methods 22 (1), 6–27. https://doi.org/10.1037/met0000086.
Moreno, F.A., Wiegand, C.B., Taitano, E.K., Delgado, P.L., 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J. Clin. Psychiatry 67 (11), 1735–1740. https://doi.org/10.4088/jcp.v67n1110.
Murphy, R., Kettner, H., Zeifman, R.J., Gibraldi, B., Kaertner, L., Martell, J., Read, T., Murphy-Beiner, A., Baker-Jones, M., Nutt, D., Erritzoe, D., Watts, R., Carhart-Harris, R.L., 2022. Therapeutic alliance and rapport modulate responses to psilocybin assisted therapy for depression. Front. Pharmacol. 12, 788155 https://doi.org/10.3389/fphar.2021.788155.
Muthukumaraswamy, S.D., Forsyth, A., Lumley, T., 2021. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert. Rev. Clin. Pharmacol. 14 (9), 1133–1152. https://doi.org/10.1080/17512433.2021.1933434.
Nour, M.M., Evans, L., Nutt, D., Carhart-Harris, R.L., 2016. Ego-dissolution and psychedelics: validation of the ego-dissolution inventory (EDI). Front. Hum. Neurosci. 269 https://doi.org/10.3389/fnhum.2016.00269.
Nutt, D., Erritzoe, D., Carhart-Harris, R., 2020. Psychedelic psychiatry's brave new world. Cell 181 (1), 24–28. https://doi.org/10.1016/j.cell.2020.03.020.
Østergaard, T., Lundgren, T., Zettle, R.D., Landrø, N.I., Haaland, V.Ø., 2020. Psychological flexibility in depression relapse prevention: processes of change and positive mental health in group-based ACT for residual symptoms. Front. Psychol. 11, 528. https://doi.org/10.3389/fpsyg.2020.00528.
Peill, J.M., Trinci, K.E., Kettner, H., Mertens, L.J., Roseman, L., Timmermann, C., Carhart-Harris, R.L., 2022. Validation of the psychological insight scale: a new scale to assess psychological insight following a psychedelic experience. J. Psychopharmacol. 36 (1), 31–45. https://doi.org/10.1177/02698811211066709.
Roseman, L., Demetriou, L., Wall, M.B., Nutt, D.J., Carhart-Harris, R.L., 2018. Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology 142, 263–269. https://doi.org/10.1016/j.neuropharm.2017.12.041.
Roseman, L., Haijen, E., Idialu-Ikato, K., Kaelen, M., Watts, R., Carhart-Harris, R., 2019. Emotional breakthrough and psychedelics: validation of the emotional breakthrough inventory. J. Psychopharmacol. 33 (9), 1076–1087. https://doi.org/10.1177/0269881119855974.
Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzo, K., Babb, J., Su, Z., Corby, P., Schmidt, B.L., 2016. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J. Psychopharmacol. 30 (12), 1165–1180. https://doi.org/10.1177/0269881116675512.
Ross, S., Agin-Liebes, G., Lo, S., Zeifman, R.J., Ghazal, L., Benville, J., Franco-Corso, S., Real, C.B., Guss, J., Bossis, A., Mennenga, S., 2021. Acute and sustained reductions in loss of meaning and suicidal ideation following psilocybin-assisted psychotherapy for psychiatric and existential distress in life-threatening cancer. ACS Pharmacol. Transl. Sci. 4 (2), 553–562. https://doi.org/10.1021/acsptsci.1c00020.
Rufino, K.A., Ellis, T.E., 2018. Contributions of cognitions, psychological flexibility, and therapeutic alliance to suicidal ideation in psychiatric inpatients. Suicide Life Threat Behav. 48 (3), 271–280. https://doi.org/10.1111/sltb.12353.
Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatry 54 (5), 573–583. https://doi.org/10.1016/S0006-3223(02)01866-8.
Rush, A.J., Bernstein, I.H., Trivedi, M.H., Carmody, T.J., Wisniewski, S., Mundt, J.C., Shores-Wilson, K., Biggs, M.M., Woo, A., Nirenberg, A.A., Fava, M., 2006. An evaluation of the quick inventory of depressive symptomatology and the Hamilton rating scale for depression: a sequenced treatment alternatives to relieve depression trial report. Biol. Psychiatry 59 (6), 493–501. https://doi.org/10.1016/j.biopsych.2005.08.022.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (20), 22–33.
Sloan, E., Hall, K., Moulding, R., Bryce, S., Mildred, H., Staiger, P.K., 2017. Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: a systematic review. Clin. Psychol. Rev. 57, 141–163. https://doi.org/10.1016/j.cpr.2017.09.002.
Sloshower, J., Skosnik, P.D., Safi-Aghdam, H., Pathania, S., Syed, S., Pittman, B., D'Souza, D.C., 2023. Psilocybin-assisted therapy for major depressive disorder: an exploratory placebo-controlled, fixed-order trial. J. Psychopharmacol. https://doi.org/10.1177/02698112311548.
Spielberger, C.D., 1983. Manual for the State–Trait Anxiety Inventory (Form Y) ("Self-Evaluation Questionnaire"). Consulting Psychologists Press.
Spielberger, C.D., 1989. State–Trait Anxiety Inventory: A Comprehensive Bibliography. Consulting Psychologists Press.
Spriggs, M.J., Douglass, H.M., Park, R.J., Read, T., Danby, J.L., de Magalhães, F.J., Alderton, K.L., Williams, T.M., Blemings, A., Lafrance, A., Nichols, D.E., Erritzoe, D., Nutt, D.J., Carhart-Harris, R.L., 2021. Study protocol for "Psilocybin as a treatment for anorexia nervosa: a pilot study". Front. Psychiatry 12, 735523. https://doi.org/10.3389/fpsyt.2021.735523.
Swift, T.C., Belser, A.B., Agin-Liebes, G., Devenot, N., Terrana, S., Friedman, H.L., Guss, J., Bossis, A.P., Ross, S., 2017. Cancer at the dinner table: experiences of psilocybin-assisted psychotherapy for the treatment of cancer-related distress. J. Humanist. Psychol. 57 (5), 488–519. https://doi.org/10.1177/0022167817715966.
Szigeti, B., Nutt, D., Carhart-Harris, R., Erritzoe, D., 2022. On the Fallibility of Placebo Control and How to Address It: A Case Study in Psychedelic Microdosing. PsyArXiv. https://doi.org/10.31234/osf.io/cjfb6.
Tennant, R., Hiller, L., Fishwick, R., Platt, S., Joseph, S., Weich, S., Parkinson, J., Secker, J., Stewart-Brown, S., 2007. The Warwick-Edinburgh mental well-being scale (WEMWBS): development and UK validation. Health Qual. Life Outcomes 5 (1), 63. https://doi.org/10.1186/1477-7525-5-63.

Thrul, J., Garcia-Romeu, A., 2021. Whitewashing psychedelics: racial equity in the emerging field of psychedelic-assisted mental health research and treatment. Drugs Educ. Prev. Policy 28 (3), 211–214. https://doi.org/10.1080/09687637.2021.1897331.

Tyndall, I., Waldeck, D., Pancani, L., Whelan, R., Roche, B., Dawson, D.L., 2019. The acceptance and action questionnaire-II (AAQ-II) as a measure of experiential avoidance: concerns over discriminant validity. J. Contextual Behav. Sci. 12, 278–284. https://doi.org/10.1016/j.jcbs.2018.09.005.

Van Spijker, B.A., Batterham, P.J., Calear, A.L., Farrer, L., Christensen, H., Reynolds, J., Kerkhof, A.J., 2014. The suicidal ideation attributes scale (SIDAS): community-based validation study of a new scale for the measurement of suicidal ideation. Suicide Life Threat Behav. 44 (4), 408–419. https://doi.org/10.1111/sltb.12084.

Watts, R., 2021. Psilocybin for Depression: The ACE Model Manual. PsyArXiv. https://doi.org/10.31234/osf.io/5x2bu.

Watts, R., Luoma, J., 2020. The use of the psychological flexibility model to support psychedelic assisted therapy. J. Contextual Behav. Sci. 15, 92–102. https://doi.org/10.1016/j.jcbs.2019.12.004.

Watts, R., Day, C., Krzanowski, J., Nutt, D., Carhart-Harris, R., 2017. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. J. Humanist. Psychol. 57 (5), 520–564. https://doi.org/10.1177/0022167817709585.

Watts, R., Kettner, H., Geerts, D., Gandy, S., Kartner, L., Mertens, L., Roseman, L., 2022. The Watts connectedness scale: a new scale for measuring a sense of connectedness to self, others, and world. Psychopharmacol 239, 3461–3483. https://doi.org/10.1007/s00213-022-06187-5.

Weston, N.M., Gibbs, D., Bird, C.I., Daniel, A., Jelen, L.A., Knight, G., Goldsmith, D., Young, A.H., Rucker, J.J., 2020. Historic psychedelic drug trials and the treatment of anxiety disorders. Depress. Anxiety 37 (12), 1261–1279. https://doi.org/10.1002/da.23065.

Wolff, M., Evens, R., Mertens, L.J., Koslowski, M., Betzler, F., Gründer, G., Jungaberle, H., 2020. Learning to let go: a cognitive-behavioral model of how psychedelic therapy promotes acceptance. Front. Psychiatry 11, 5. https://doi.org/10.3389/fpsyt.2020.00005.

Wolff, M., Mertens, L.J., Walter, M., Enge, S., Evens, R., 2022. The Acceptance/Avoidance-promoting experiences questionnaire (APEQ): a theory-based approach to psychedelic drugs' effects on psychological flexibility. J. Psychopharmacol. 36 (3), 387–408. https://doi.org/10.1177/02698811211073758.

Yela, J.R., Crego, A., Gómez-Martínez, M.Á., Jiménez, L., 2020. Self-compassion, meaning in life, and experiential avoidance explain the relationship between meditation and positive mental health outcomes. J. Clin. Psychol. 76 (9), 1631–1652. https://doi.org/10.1002/jclp.22932.

Zeifman, R.J., Wagner, A.C., Watts, R., Kettner, H., Mertens, L.J., Carhart-Harris, R.L., 2020. Post-psychedelic reductions in experiential avoidance are associated with decreases in depression severity and suicidal ideation. Front. Psychiatry 11, 782. https://doi.org/10.3389/fpsyt.2020.00782.

Zeifman, R.J., Dengdeng, Y., Singhal, N., Wang, G., Nayak, S.M., Weisman, C.R., 2022a. Decreases in suicidality following psychedelic therapy: a meta-analysis of individual patient data across clinical trials. J. Clin. Psychiatry 83 (2), 39235. https://doi.org/10.4088/JCP.21r14057.

Zeifman, R.J., Spriggs, M.J., Kettner, H., Carhart-Harris, R., 2022b. RElaxed Beliefs-Questionnaire (REB-Q) and REB-Q Self-Report (REB-Q-SR): Administration Manual. PsyArXiv. https://doi.org/10.31234/osf.io/r597a.

Zeifman, R.J., Spriggs, M.J., Kettner, H., Lyons, T., Rosas, F., Mediano, P., Erritzoe, D., Carhart-Harris, R., 2022. From Relaxed Beliefs Under Psychedelics (REBUS) to Revised Beliefs After Psychedelics (REBAS): Preliminary Development of the RElaxed Beliefs Questionnaire (REB-Q). PsyArXiv. https://doi.org/10.31234/osf.io/w8j6t.