Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety

Alan K. Davis[a,b,*], Frederick S. Barrett[b], Roland R. Griffiths[b,c]

[a] College of Social Work, The Ohio State University, Columbus, OH, 43210, USA
[b] Center for Psychedelic and Consciousness Research, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD, 21224, USA
[c] Department of Neuroscience, Johns Hopkins School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD, 21224, USA

ABSTRACT

Prior research has shown that acute subjective psychedelic effects are associated with both spontaneous and intended changes in depression and anxiety. Psychedelics are also theorized to produce increases in psychological flexibility, which could explain decreases in depression and anxiety following a psychedelic experience. Therefore, the present cross-sectional survey study sought to examine whether psychological flexibility mediated the relationship between acute psychedelic experiences and spontaneous or intended changes in depression and anxiety among a large international sample of people who reported having used a psychedelic (n = 985; male = 71.6%; Caucasian/white = 84.1%; M_{age} = 32.2, SD = 12.6). A regression analysis showed that acute effects (i.e., mystical and insightful effects) were significantly associated with decreases in depression/anxiety following a psychedelic experience. A path analysis revealed that, while controlling for age and sex, increases in psychological flexibility fully mediated the effect of mystical and insightful experiences on decreases in depression and anxiety following a psychedelic experience. This suggests that psychological flexibility may be an important mediator of the therapeutic effects of psychedelic drugs. Future prospective experimental studies should examine the effect of psychedelic drug administration on psychological flexibility in order to gain a better understanding of the psychological processes that predict therapeutic effects of psychedelics.

1. Introduction

Depression and anxiety disorders are common mental health problems (Steel et al., 2014). Global lifetime prevalence of depression and anxiety are approximately 10% and 13%, respectively (Steel et al., 2014; Bandelow and Michaelis, 2015). The public health burden of depression and anxiety includes occupational impairment (Birnbaum et al., 2010), and increases the risk for chronic physical conditions such as cardiovascular disease (Katon, 2011; Niles et al., 2015). Given high prevalence rates and the substantial public health and personal burden

of these mental health conditions, numerous interventions have been developed, which include combinations of psychotherapy and pharmacotherapy (Cuijpers et al., 2014; Otto and Hearon, 2016). Despite evidence supporting the use of these interventions, many people do not have access to these treatments (Collins et al., 2004), and many people who have access will not experience symptom relief despite intervention (Collimore and Rector, 2014; Coull and Morris, 2011; Hofmann et al., 2012; Sinyor et al., 2010; Koen and Stein, 2011), highlighting the need for more treatment options.

One emerging area of research has examined the psychotherapeutic action of psychedelic compounds (e.g., psilocybin, LSD, ayahuasca, 5-MeO-DMT) administered in clinical trials (Carhart-Harris et al., 2016; Johnson and Griffiths, 2017; Palhano-Fontes et al., 2018; dos Santos et al., 2016) and used in naturalistic settings (Davis et al., 2018, 2019; Johnson et al., 2017). These substances act primarily as agonists of serotonin (e.g., 5-HT1A/2A/C) receptors and often produce profound changes in sensory perceptions, mood, cognitions, and behavior (Araújo et al., 2015; Carhart-Harris et al., 2011; Stroud et al., 2017; Carhart-

Harris et al., 2017; dos Santos et al., 2016). For example, recent studies examining psychedelics administered as an adjunct to psychotherapy have demonstrated efficacy in decreasing symptoms of anxiety and depression (Johnson and Griffiths, 2017; Carhart-Harris et al., 2017; Ross et al., 2016; Griffiths et al., 2016; dos Santos et al., 2016). Published reports also show that decreases in depression and anxiety occur following naturalistic psychedelic use in ceremonial and recreational contexts (Davis et al., 2018,2019; Santos et al., 2007; Uthaug et al., 2018). Although more work is needed to fully understand the mechanisms of therapeutic action, the beneficial effects of these substances appear to be associated with the intensity of certain types of acute psychedelic effects (e.g., mystical-type phenomena, psychological insight) during these experiences in both healthy (Griffiths et al., 2008, 2011; Barrett et al., 2015) and clinical (Ross et al., 2016; Griffiths et al., 2008, 2011, 2016; Roseman et al., 2018; Davis et al., 2018; Garcia-Romeu et al., 2019) populations. Potential mediators of psychedelic effects on therapeutic outcomes have been suggested, including changes in the entropy of brain network connectivity (Carhart-Harris et al., 2014), the importance of awe/ego dissolution (Hendricks, 2018; Preller and Vollenweider, 2018); and the possible role of changes in psychological flexibility following a psychedelic experience (Kuypers et al., 2016; Sabucedo, 2017; Walsh and Thiessen, 2018).

Psychological flexibility is described as an essential set of processes that help people manage stressors and engage in adaptive behaviors that promote values-driven action (Gloster et al., 2017). Psychological flexibility is a transdiagnostic construct wherein people are thought to have the capacity to develop skills recognizing and adapting to various contextual demands, shift their mindset or behaviors during individual and social experiences, maintain balance across important life domains, and learn to be open to, aware of, and committed to behaviors that are congruent with their values (Kashdan and Rottenberg, 2010). According to this model, well-being is supported by fully contacting the present moment as a conscious human being and changing or persisting in a values-driven behavior regardless of what is present in each moment (Hayes et al., 2012). Conversely, dysfunctions in mental health, including depression and anxiety disorders (Kashdan and Rottenberg, 2010), are theorized to be the result of reduced psychological flexibility (or psychological *in*flexibility).

Psychological interventions have been developed using this theoretical framework (e.g., Acceptance and Commitment Therapy (ACT); Hayes et al., 2006), which attempt to increase psychological flexibility via six interconnected processes (i.e., acceptance, defusion, being present, self-as-context, determining direction for behavior change, and using techniques to facilitate change; Twohig and Levin, 2017). Meta-analyses have shown moderate to strong effects in favor of ACT interventions (compared to control conditions: waitlist, psychological placebo, and treatment as usual) in decreasing anxiety and depression symptoms (A-Tjak et al., 2015; Hacker et al., 2016), and evidence shows that the positive outcomes of this intervention are mediated by increases in psychological flexibility (French et al., 2017; Twohig and Levin, 2017). If psychedelic experiences promote increases in psychological flexibility, then such increases could be mediating the antidepressive and anxiolytic effects observed in clinical trials (Johnson and Griffiths, 2017; Carhart-Harris et al., 2017; Ross et al., 2016; Griffiths et al., 2016; dos Santos et al., 2016) and the associations found in naturalistic psychedelic use (Davis et al., 2018, 2019; Santos et al., 2007; Uthaug et al., 2018). This relationship could also justify a psychotherapeutic approach to psychedelic-assisted therapy that focuses on processes of change with the psychological flexibility model.

The present cross-sectional survey study sought to examine psychological flexibility as a potential mediator of acute psychedelic experiences on changes in anxiety/depression. Prior research has shown that acute psychedelic effects are associated with reductions in depression and anxiety (Davis et al., 2019; Griffiths et al., 2016; Ross et al., 2016), that psychedelic effects are associated with changes in psychological flexibility (Kuypers et al., 2016), and that increases in

psychological flexibility are associated with positive depression and anxiety outcomes (Twohig and Levin, 2017). Therefore, in a regression model we expect to find (Hypothesis 1: H1) acute psychedelic effects (mystical and insight effects) will predict changes in depression and anxiety following a psychedelic experience, and in a path model we expect to find that H2) acute psychedelic effects will be directly related to increases in psychological flexibility, H3) increases in psychological flexibility will be directly related to decreases in depression/anxiety, and H4) psychological flexibility will mediate the relationships between acute psychedelic effects and decreases in depression and anxiety symptoms.

2. Method

2.1. Procedure

The current study data were collected as part of a large anonymous internet-based cross-sectional survey of individuals who reported having a moderate to strong psychedelic experience in the past. Specifically, people were recruited as part of a larger study examining acute insight (e.g., an awareness into emotions, behaviors, beliefs, memories, relationships, etc.) gained as a result of a psychedelic experience. Recruitment from the parent study is ongoing and results will be published in a forthcoming article. Respondents were recruited by using electronic message postings and advertisements on several internet websites (e.g., www.erowid.com; www.facebook.com; www.reddit.com), electronic mail announcements, and via an article published by Motherboard/VICE. Advertisements directed potential respondents to a secure web-based survey (hosted by: www.qualtrics.com), and those who clicked a study link were presented with a consent document detailing the inclusion criteria. Eligible volunteers had to endorse being at least 18 years old, able to read, write and speak English fluently, have taken a dose of a single psychedelic (e.g., psilocybin mushrooms, psilocybin, LSD, ayahuasca, mescaline, N,N-DMT, 5-MeO-DMT, peyote, 4-Acetoxy-DMT, Salvia, Ibogaine, etc.) that produced moderate to strong psychoactive effects, and after taking the substance they must have had an experience that contributed to gaining psychological insight. Following consent, respondents completed each study questionnaire (described below). The study was approved by the Johns Hopkins School of Medicine Institutional Review Board and the full survey is available from the corresponding author. No incentives were offered in this study.

2.2. Study recruitment flow

Respondents were recruited from June 2018 through January 2019. Of all individuals who clicked the advertisement link (n = 14,911), 3080 consented and completed the survey. However, 960 of these respondents were excluded because they reported using more than one substance in their psychedelic experience. Of the remaining 2120, a total of 985 were included in the final sample because they indicated experiencing a change in anxiety or depression as a result of a psychedelic experience.

3. Measures

3.1. Psychedelic experience

We asked respondents to report which psychedelic substance they had used (e.g., psilocybin, LSD, N,N-DMT, Ayahuasca, 5-MeO-DMT, Mescaline, Salvia/Salvinorin A, peyote cactus, Iboga/ibogaine, or "Other"), the subjective level of dose (i.e., Low, Moderate, Moderately high, High), route of administration (i.e., Oral, Sublingual, Smoked or Vaporized, Buccal, Intravenous, Intranasal), and length of time since the experience (e.g., 3–6 months ago, 7–11 months ago, 1–2 years ago, etc.).

3.2. Acute mystical experiences

The Mystical Experiences Questionnaire (MEQ) was used to assess subjective mystical-type phenomena that may have occurred after taking the psychedelic (Maclean et al., 2012; Barrett et al., 2015). Respondents were asked to think back on their experience with a psychedelic and then to rate the extent to which each of 30 descriptors applied at any point during their session on a 6-point scale from 0 = "None; not at all" to 5 = "Extreme (more than ever before in my life)." Similar to prior research (Davis et al., 2018, 2019), we calculated a total mean score of all items on the questionnaire. Internal consistency reliability of the total scale was excellent (alpha = .94).

3.3. Acute insight experiences

The Psychological Insight Questionnaire (PIQ) was created to assess the degree to which respondents experienced acute insight (e.g., gained an awareness into your emotions, behaviors, beliefs, memories, or relationships) that sometimes occurs after taking a psychedelic. Respondents were asked to think back on their experience with a psychedelic and then to rate the intensity with which they experienced each of 28 insight experiences at any point during their session, and similar to the MEQ they rated each item on a 6-point scale from 0 = "No; not at all" to 5 = "Extremely (more than ever before in my life)." A total score was calculated as the mean of the responses to each item, and the internal reliability of this total score was excellent (alpha = .93). The PIQ is under development and the psychometric properties of this questionnaire will be reported in a forthcoming manuscript. See Table 1 for items, item means (and standard deviations), and percent endorsement of each item ('No, not at all' = 0 and all other response options = 1).

3.4. Anxiety and depression

The Depression, Anxiety, and Stress Scale (DASS-21) was used to assess for anxiety and depression symptoms during the 3 months *before* and 3 months *after* the psychedelic experience. This 21-item scale (Lovibond and Lovibond, 1995) examines the core negative emotional experiences of depression and anxiety that respondents reported experiencing. The DASS-21 is comprised of three subscales: depression, anxiety, and stress, of which we used a subscale consisting of the combined depression and anxiety subscales in the current study. There are seven items in each subscale and respondents are asked to respond to each item on a scale from 0 = "Never" to 3 = "Almost always." Internal consistency reliability was good for the *before* measures (depression subscale alpha = .91; anxiety subscale alpha = .80) and adequate-to-good for the *after* measures (depression subscale alpha = .84; anxiety subscale alpha = .69). In the present study, we examined subjective changes in depression and anxiety following a psychedelic experience by calculating a mean total change score by subtracting the total depression and anxiety *after* scores from the total depression and anxiety *before* scores for each respondent (e.g., negative scores represent a decrease in depression/anxiety). A single measure combining depression and anxiety subscales (depression/anxiety) was analyzed as the dependent measure in analyses reported in this report. Separate analyses for depression and anxiety subscales are reported in supplementary material.

3.5. Psychological flexibility

The Acceptance and Action Questionnaire II (AAQII; Bond et al., 2011) was developed as a measure of psychological *in*flexibility, and in the present survey it was used to assess the degree of psychological flexibility respondents experienced *before* and *after* the psychedelic experience. The AAQII is comprised of 7 items and respondents were asked to respond to each item on a scale from 1 = "Never true" to

Table 1
Psychological Insight Questionnaire item means and standard deviations (*N* = 985).

Item	Mean(SD)	Proportion of sample that endorsed at any intensity level[a]
Realized how current feelings or perceptions are related to events from my past	3.51 (1.52)	93.1%
Awareness of uncomfortable or painful feelings I previously avoided	3.17 (1.67)	88.1
Realized ways my beliefs may be dysfunctional	3.53 (1.55)	91.4
Discovered how aspects of my life are affecting my well-being	3.93 (1.21)	97.6
Gained a deeper understanding of events/memories from my past	3.48 (1.52)	93.4
Experienced validation of my life, character, values, or beliefs	3.71 (1.43)	94.5
Realized the importance of my life	3.84 (1.48)	92.8
Awareness of dysfunctional patterns in my actions, thoughts, and/or feelings	3.66 (1.43)	94.2
Discovered specific techniques for coping with difficulties	3.19 (1.57)	90.6
Realized how critical or judgmental views I hold towards myself are dysfunctional	3.58 (1.50)	93.3
Discovered I could explore uncomfortable or painful feelings I previously avoided	3.47 (1.55)	91.7
Gained a deeper understanding of previously held beliefs and/or values	3.84 (1.27)	97.1
Discovered a vivid sense of the paradoxes in life	3.63 (1.57)	92.0
Realized I could experience memories previously too difficult to experience	2.37 (1.86)	72.9
Awareness of beneficial patterns in my actions, thoughts, and/or feelings	3.29 (1.45)	93.1
Discovered a clear pattern of avoidance in my life	2.76 (1.72)	83.1
Realized the nature and/or origins of my defenses or other coping strategies	3.04 (1.63)	88.0
Discovered new insights about my work or career	2.29 (1.88)	70.6
Gained resolution or clarity about past traumas or hurtful events	2.91 (1.78)	83.6
Discovered clear similarities between my past and present interpersonal relationships	2.83 (1.74)	83.1
Discovered new feelings or perspectives about significant relationships in my life	3.65 (1.48)	93.0
Realized certain actions I should take in regards to important relationships in my life	3.42 (1.56)	91.4
Discovered new actions that may help me achieve my goals	3.28 (1.53)	91.7
Realized the point of view or actions of others that had been difficult to understand previously	3.25 (1.61)	89.7
Discovered clarity or creative solutions about how to solve a problem in my life	3.28 (1.55)	91.7
Awareness of information that helped me understand my life	4.14 (1.14)	97.8
Discovered ways to see my problems with more clarity	3.81 (1.30)	96.0
Awareness of my life purpose, goals, and/or priorities	3.77 (1.42)	94.7

Note. Range of scores of all items was 0–5.

[a] Response options were on a scale from 0 = "No, Not at all" to 5 = "Extremely (more than ever before in my life)". Data in this column show the proportion of respondents who endorsed any option other than "No, Not at all.".

Table 2
Means, standard deviations, and correlations among variables included in path analysis (i.e., mystical experiences score, psychological insight score, depression/anxiety symptom change score, psychological flexibility ch^{a}nge score; $N = 985$).

	M (SD)	1	2	3	4	5	6
1. Age	32.19 (12.6)		07	.09	-.09	.14	-.07
2. Sex[a]	1.27 (0.45)			.09	.01	-.06	.08
3. Mystical Experiences	3.80 (0.89)				.41	-.19	**.28**
4. Psychological Insight	3.38 (0.91)					**-.31**	**.50**
5. Decrea^{a}e in anxiety/depression	−6.80 (5.61)						**-.62**
6. Increase in psychological flexibility[b]	2.09 (1.44)						

Note. Bolded items were considered statistically significant (p < .001) and meaningful (coefficient > 0.20).
  [a] Sex coded Male = 1, Female = 2.
  [b] The AAQII was originally developed as a measure of psychological inflexibility. Reduction in AAQ scores indicates an increase in psychological flexibility. However, to ease interpretation, we have calculated a positive change score to denote increases in psychological flexibility.

7 = "Always true." Lower scores on this measure indicate greater psychological flexibility. Internal consistency reliability was good for the psychological flexibility *before* measure (alpha = .88) and the psychological flexibility *after* measure (alpha = .88). We examined changes in psychological flexibility by calculating a mean change score. This calculation involved subtracting the mean psychological flexibility *before* score from the mean psychological flexibility *after* score for each respondent in order to ease interpretation (i.e., we calculated a positive change score to denote *increases* in psychological flexibility). This change score was used in all analyses.

3.6. Demographics

We included items inquiring about the age, sex, gender, race, ethnicity, country/region of residence, income, level of education, and relationship status of each respondent.

3.7. Data analyses

Data Quality. Study completion time was examined in order to identify cases of rushed and possibly careless responding. Overall, respondents completed the survey in approximately 47 min. Only 3 respondents took less than 15 min to complete the survey; 25% of the sample completed the survey in less than approximately 33 min; and 75% of the sample completed the survey in less than approximately 67 min. Although 3 respondents completed the survey in less than 15 min, a review of their responses did not provide any indication of careless responding. This pattern of response time suggests that careless responding was not a concern.

Analytic Plan. First, descriptive statistics for demographic and background characteristics for all study variables were calculated. Pearson and point biserial correlation coefficients were calculated to examine the relationships among all primary study variables (age, sex, acute insight and mystical effects, depression/anxiety change score, and psychological flexibility change score). Given the large number of respondents in the sample, we used a coefficient cutoff of 0.20, and used an alpha cutoff of $p < .001$, to determine whether a correlation was both meaningful and statistically significant, respectively. Next, a regression analysis was used to test (H1): acute mystical and insight experiences will be negatively associated with depression/anxiety change score. A path analysis was then used to test hypothesized direct effects (H2–H3: Intensity of psychological insight and mystical effects have a direct effect on changes in psychological flexibility, and changes in

psychological flexibility have a direct effect on changes in depression/anxiety) and mediation effects (H4): Intensity of psychological insight and mystical effects are indirectly related to changes in depression/anxiety via and the path analyses. Analyses were conducted in SPSS v 25 (IBM Corp, 2018) and MPlus version 7.0 using weighted least square mean and variance estimators (Muthén and Muthén 1998-2017).

4. Results

4.1. Respondent characteristics

Most of the sample reported they were male (72%), Caucasian/white (84%), never married (51%), currently live in the United States (65%) and earned $35,000 or more in income (60%). Average age in the sample was 32.2 (SD = 12.6). Over three-quarters of the sample reported that their psychedelic experience was occasioned by LSD (42%) or psilocybin/mushrooms (38%) as the psychedelic substance used to occasion their experience. Furthermore, about one-half of the sample reported that the dose was moderately-high (36%) or high (21%). The psychedelic experience had occurred at least 1 year prior to the survey in 75% of the sample. Overall, there was a mean decrease in depression/anxiety ($M = -6.80$; $SD = 5.61$; Range: -21 to $+9$), and a mean increase in psychological flexibility ($M = 2.01$; $SD = 1.44$; Range: -4.14 to $+6$), from before to after the psychedelic experience. Additional details about respondent characteristics are shown in Supplemental Table 1.

Associations between acute psychedelic effects and psychological flexibility and depression/anxiety change scores.

A series of point-biserial correlations revealed that the type of psychedelic drug used by respondents (Psilocybin: No = 0, Yes = 1; LSD: No = 0, Yes = 1; Other Psychedelic: No = 0, Yes = 1) was unrelated (range: -0.19 to 0.14) to all other variables (age, sex, acute insight and mystical effects, depression/anxiety change score, and psychological flexibility change score). Additionally, as Table 2 shows, the intensity of mystical effects was moderately correlated with insight effects and to a lesser degree with decreases in depression/anxiety and increases in psychological flexibility. Intensity of psychological insight was moderately correlated with decreases in depression/anxiety; and the intensity of psychological insight and decreases in depression/anxiety were correlated with increases in psychological flexibility.

4.2. Regression analysis

Table 3 shows data from the multiple linear regression including acute mystical ($M = 3.81$; $SD = 0.89$) and insight effects ($M = 3.38$; $SD = 0.91$) as predictors of decreases in depression/anxiety ($M = -6.80$; $SD = 5.61$). The overall model was significant ($p < .001$), accounting for 10% of the variance in depression/anxiety change scores (H1). Although accounting for a relatively small amount of variance in this model, the intensities of both mystical and insight effects were associated with decreases in depression/anxiety (see Table 3).

Table 3
Summary of multiple linear regression showing significant predictors of changes in depression or anxiety (spontaneous and intended) from before to after a psychedelic experience ($N = 985$).

Variables	B	SE B	β	t	p
Constant	.90	.83			
Mystical effects	-.51	.21	-.08	−2.428	.015*
Psychological insight effects	−1.71	.20	-.28	−8.395	.000***
Adjusted R^2		.10			

Note. The overall model was significant, $F(2, 984) = 55.675$, $p < .001$.
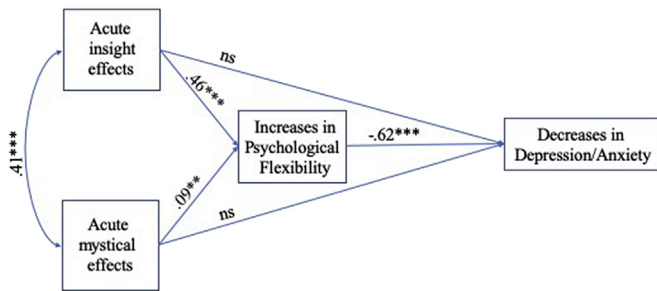*$p < .05$; ***$p < .001$.

Fig. 1. Path analysis showing that increases in psychological flexibility mediate relationship between acute effects of psychedelics and decreases in depression/anxiety (full sample, N=985). **p < .01, ***p < .001.

4.3. Path analysis

As shown in Fig. 1, the path analysis controlling for age and sex revealed that greater mean intensity of acute mystical and psychological insight effects were directly related (Mystical: $\beta = 0.09$, p < .01; Insight: $\beta = 0.46$, p < .001) to mean increases in psychological flexibility ($M_{increase} = 2.09$; $SD = 1.44$; supporting H2), mean increases in psychological flexibility were directly related ($\beta = -0.62$, p < .001) to mean decreases in depression/anxiety (supporting H3), and indirect effects were found wherein psychological flexibility mediated the relationships between the intensity of acute mystical ($\beta = 0.06$, SE = 0.02, $p < .01$) and insight ($\beta = 0.29$, SE = 0.02, $p < .001$) effects and mean decreases in depression/anxiety (supporting H4). Model fit was good: root mean square error of approximation = .055 (95% CI: 0.01, 0.12); comparative fit index = 0.995; weighted root-mean-square residual = 0.394.

4.4. Supplementary analyses

The sample used for our primary analyses (described above) was a group of individuals who reported a spontaneous or intended change in anxiety (intended $N = 142$; spontaneous $N = 197$) or depression (intended $N = 366$; spontaneous $N = 280$) following a psychedelic experience. In the path analysis shown in Fig. 1, we collapsed these groups into one sample ($N = 985$), and averaged measures of depression and anxiety into a single measure, in order to examine our primary study hypotheses in a more concise manner. However, we also analyzed all study hypotheses (H1–H4) within each of these subgroups using the same analytic approach described above, and these tables and figures are available in supplementary files (Suppl. Tables 1-4; Suppl. Figures 1-4). In short, all hypotheses were replicated in each subsample, with two notable exceptions. Among those who *intended* to change their anxiety after a psychedelic experience, the regression analyses (Suppl. Table 3) showed that intensity of mystical effects was *not* significantly associated with decreases in anxiety (contrary to H1). Furthermore, in the path analysis (Suppl. Figure 3), intensity of mystical effects was *not* significantly associated with increases in psychological flexibility (contrary to H2), nor were there indirect relationships between acute mystical effects and decreases in anxiety via increases in psychological flexibility. However, all other findings showed that our models were identical regardless of whether one had a spontaneous or intended change in these their anxiety/depression.

5. Discussion

The present retrospective cross-sectional survey study examined whether psychedelic occasioned mystical-type or psychological insight experiences predicted decreases in depression and anxiety following a psychedelic experience (H1), acute psychedelic effects predicted increases in psychological flexibility (H2), increases in psychological flexibility predicted decreases in depression/anxiety, (H3) and whether

increases in psychological flexibility mediated the relationships between acute psychedelic effects and decreases in depression and anxiety symptoms (H4). Findings from our regression and path analysis models supported each of these hypotheses. Consistent with prior studies (Davis et al., 2019; Griffiths et al., 2016; Ross et al., 2016), in the present study mystical experiences were associated with decreases in depression and anxiety. Importantly, these observations were extended by showing that experiences of psychological insight during a psychedelic experience are also associated with decreases in depression and anxiety. Further, when mystical and psychological insight effects were included simultaneously as predictors of changes in our models, results showed that psychological insight stands out as a more robust predictor of change, as evidenced by the larger direct (Insight: $\beta = 0.46$ versus Mystical: $\beta = 0.09$) and indirect (Insight: $\beta = 0.29$ versus Mystical: $\beta = 0.06$) coefficients in the path analysis.

That psychological insight is strongly related to decreases in depression and anxiety is perhaps not surprising given the history of insight-oriented therapies (Connolly Gibbons et al., 2007), but it has also been questioned whether gaining insight is sufficient in and of itself to produce lasting changes in behavior or mental health functioning (Kuncewicz et al., 2014; Leichsenring et al., 2006). To this point, our models also showed that psychological insight was predictive of change when accounting for the correlation between insight and mystical experiences. Insightful as well as mystical-type experiences have been identified as subtypes of the phenomenon of *quantum change*, which refers to a sudden, distinctive, benevolent, and enduring experience resulting in personal transformations that affect a broad range of personal emotions, cognitions and behaviors (Miller and C'de Baca, 2001; Miller, 2004). Such experiences after taking a psychedelic have also been implicated in decreases in alcohol use among individuals with alcohol use disorder (Garcia-Romeu et al., 2019).

Furthermore, findings from the present study underscore a potential explanation for *how* acute psychedelic experiences, including gaining psychological insight and mystical experiences, may exert such changes. Specifically, we demonstrated the importance of increases in psychological flexibility as a mediator of the positive therapeutic effects. Although several other mechanisms have been proposed at various levels of functioning, from changes in the entropy of brain network connectivity (Carhart-Harris et al., 2014) to the importance of awe/ego dissolution (Hendricks, 2018; Preller and Vollenweider, 2018), findings from this study are consistent with evidence demonstrating that psychedelic effects are associated with changes in psychological flexibility among a small sample of subjects who use the psychedelic ayahuasca (Kuypers et al., 2016), and research showing that increases in psychological flexibility is associated with positive depression and anxiety outcomes (Twohig and Levin, 2017).

Although the exploration of potential mediators of psychedelic effects on therapeutic outcomes is in its early stages, if psychological flexibility emerges as a consistent and robust mediator of effects in prospective clinical trials, then the field of psychedelic-assisted psychotherapy should consider integrating psychedelic administration with contextual behavioral therapies (e.g., ACT; Hayes et al., 2006) or other therapies designed to target psychological flexibility. Such therapies are designed to enhance processes of change by supporting increases in psychological flexibility which could be enhanced through the administration of a psychedelic. Moreover, it is possible that some acute psychedelic effects overlap with the core processes of the ACT model of psychopathology (Hayes et al., 2006). For example, consistent with the core processes of ACT, qualitative analysis of first-hand accounts of tobacco smokers in a clinical trial examining the effect of psilocybin-assisted therapy (Johnson et al., 2014; Noorani et al., 2018), suggested that their psychedelic experiences helped them see themselves in the context of their addiction (i.e., self as context), realize that they are not the labels (e.g., smoker) which they previously identified as (i.e., defusion), understood their values more clearly than before (i.e., values), and connected with the fullness of the present moment

and their experience of it (i.e., contact with the present moment). Although not highlighted in the qualitative reports per se, another component of the ACT model, committed action, was demonstrated in the clinical trial by the high rates (80%) of biologically verified abstinence at 6 months post-treatment (Johnson et al., 2014). These data suggest that psychedelics appear to occasion both mindfulness/acceptance processes as well as commitment and behavior change processes. However, more research is needed to systematically investigate these processes in rigorous longitudinal trials among individuals with depression or anxiety in order to replicate these findings in this population.

This study has several limitations. Internet-based recruitment and data collection procedures were anonymous. Although this likely increased participation from individuals from a variety of geographical locations, it would have excluded people who are unable or prefer not to participate in research conducted on the internet. Further, a limitation of survey methods is that all reports are retrospective, increasing the likelihood that current affect and personality bias could influence recollection of subjective psychedelic experiences as well as depression and anxiety symptoms that were experienced many years ago. However, this potential confound is not expected to be more or less than similar confounds in other retrospective survey research (Davis et al., 2018,2019). Additionally, the parent study from which the data were drawn, was designed to investigate the acute effect of gaining insight during a psychedelic experience. Although the mean score of the intensity of mystical experiences in this sample was similar to prior studies (Davis et al., 2018), suggesting comparably strong mystical effects in addition to insight effects, we cannot rule out the possibility that recruiting people who specifically reported gaining insight as part of a psychedelic experience accounts for some of the differential strength in the association between acute insight and other study variables.

Another limitation to this study is that, despite our efforts to recruit individuals with diverse backgrounds by placement of notices on a variety of internet forums, respondents were primarily young, white, and male. Although our sample is consistent with prior studies of psychedelic users using similar recruitment procedures (Barrett et al., 2016; Davis et al., 2018), similar to Michaels et al. (2018) we strongly encourage future researchers to continue efforts in recruiting a diverse sample. There are several possible explanations for the lack of diverse representation in psychedelic survey studies. For example, it could be that the topic of these studies are not interesting to some potential respondents, that there is a perceived risk involved with reporting an illegal behavior, or that the internet computer format excluded individuals from differing socio-economic backgrounds. Efforts to overcome these factors could include a community-based participatory research methodology (Israel et al., 2005), wherein the study is designed through engagement with leaders from a variety of diverse backgrounds, with the intention of better understanding the ways in which the study can be designed to connect with individuals from these communities.

6. Conclusion

The findings from the present study highlight the role of psychological flexibility as a mediator of acute psychedelic effects and decreases in depression/anxiety. Future studies should examine the effect of psychedelic drug administration on psychological flexibility in a laboratory setting using a controlled trial design in order to ascertain the causal influences of psychological processes that predict therapeutic effects of hallucinogens. Such work should include measurement of the core processes of ACT (e.g., defusion, values, self as context, etc.) in order to examine whether changes in these core processes occur and predict enduring effects of psychedelic substances on therapeutic outcomes. If psychological flexibility continues to be shown to mediate positive therapeutic outcomes, future research should explore whether

such therapeutic effects can be further enhanced by using a psychotherapeutic approach to psychedelic-assisted therapy that specifically targets processes of change within a transdiagnostic psychological flexibility model.

Declaration of competing interests

Dr. Griffiths is a board member of Heffter Research Institute and Dr. Davis is a board member of Source Research Foundation. Neither organization was involved in the design/execution of this study or the interpretation or communication of findings.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcbs.2019.11.004.

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