5-MeO-DMT as a Mental Health Tool: Exploring Possible Mechanisms of Action, the Reactivation Phenomenon, and Historical-Cultural Perspectives on Its Use

by

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Abstract

The short-acting psychedelic 5-MeO-DMT is gaining attention as a novel treatment for psychiatric disorders. Given the current interest in this substance, this dissertation investigated three different relevant aspects related to 5-MeO-DMT. Manuscript 1 examined potential psychological mechanisms underlying 5-MeO-DMT's therapeutic effects. A cross-sectional survey of participants (n = 90, Mean age = 38.8) assessed changes in the psychological constructs of cognitive fusion, nature relatedness, and prosocial behavioral intentions before and after 5-MeO-DMT use. Significant decreases in cognitive fusion and increases in nature relatedness and prosocial intentions were noted, particularly associated with challenging and insightful experiences.

Manuscript 2 explored the prevalence, predictors, and emotional valence of a complex and poorly understood phenomenon known as "reactivations" following 5-MeO-DMT use (n = 90, Mean age = 38.8). Reactivations were found to be common and predominantly experienced as positive or neutral events. Predictors of reactivation experiences were the amount of time planned ahead for a 5-MeO-DMT dose, and decreases in cognitive fusion from before-to-after 5-MeO-DMT use. Psychological insight effects were associated with greater likelihood of reactivations being perceived positively, while challenging effects were associated with lower likelihood of positive/neutral emotional valence.

Manuscript 3 provided a comprehensive historical and cultural analysis of 5-MeO-DMT use, tracing its origins to ancient South American Indigenous practices. It also examined the symbolic significance of a toad motif among Mesoamerican cultures, and discussed modern applications of toad-derived 5-MeO-DMT in North America and globally. This historical-

cultural perspective provides crucial context for understanding the current therapeutic interest in 5-MeO-DMT and the ethical considerations surrounding its use and sourcing.

Taken together, this dissertation's findings contribute to the scientific literature on 5-MeO-DMT's potential psychological mechanisms of action, and provide helpful data regarding the reactivation phenomenon. Additionally, it provides a comprehensive historical-cultural perspective on 5-MeO-DMT use from ancient practices to modern applications, offering insights into the evolving cultural and societal perceptions of this compound and its potential role as a mental health tool.

Table of Contents

Chapter 1 - Introduction

In recent years, psychedelic substances have taken the world by storm (Raison, 2018). A few short decades ago, to want to conduct mental health research with psychedelic substances was considered to be professional and/or academic suicide. Starting in the early 2000s however, psychedelics began slowly, but increasingly, to be looked upon as potentially effective tools in the treatment of various psychiatric disorders including depression, anxiety, substance use disorders and obsessive-compulsive disorder (Bogenschutz et al., 2015; Bogenschutz et al., 2022; Carhart-Harris et al., 2016; Carhart-Harris & Goodwin, 2017; Davis, Barrett, May, et al., 2021; Goodwin et al., 2022; Griffiths et al., 2016; Johnson et al., 2014; Johnson et al., 2019; Luoma, Chwyl, et al., 2020; Moreno et al., 2006; Moreton et al., 2022; Ross et al., 2016).

Even though there was steady research with psychedelics in the 1950s and 1960s, in 1970 research almost completely came to a halt due to the establishment of the Controlled Substances Acts (CSA). The CSA placed psychedelic drugs in Schedule 1, thus classifying them as substances of high addictive potential, and no therapeutic benefit (Belouin & Henningfield, 2018; Reiff et al., 2020).

At the time of this writing however, psychedelic substances are becoming one of the fastest growing areas of research in prestigious academic institutions around the globe, and research centers dedicated exclusively to investigating the therapeutic potential of these drugs are being, or have been set up, at places such as Harvard University, Johns Hopkins University, Yale University, University of California - San Francisco, University of California - Berkeley, Emory University, the Ohio State University, the University of Wisconsin-Madison, and many more in the United States and abroad.

Based on the positive results from academic studies to date, psilocybin is steadily moving along the path of regulatory approval as a treatment for major depressive disorder, under the auspices of the Food and Drug Administrations'(FDA) *Breakthrough Therapy Designation*. Created through the FDA's Safety and Innovation Act of 2012, this approval pathway is designed to shorten the development and review time of promising new drugs that have shown preliminary, but substantial improvements over best available treatments for specific conditions (Eisenstein, 2022).

Significance

Taking into consideration the amount of cultural stigma associated with psychedelic substances, a stigma that for several decades significantly impeded scientific research with these drugs (Belouin & Henningfield, 2018), it is remarkable to see the exponentially growing interest they have generated over the past 10 years, and which has really intensified in the last five.

What may be driving this growing interest? It could be reasonably argued that there are two lines of evidence that are fueling this burgeoning explosion of interest. First, the fact that despite best available current treatments there are very high rates of non-response and relapse in various mental health disorders, including major depressive disorder and anxiety disorders, underscoring a significant unmet clinical need (Burcusa & Iacono, 2007) that represent a major public health burden (Malhi & Mann, 2018). Second, mounting evidence shows that psychedelic drugs can be robustly effective and efficacious in treating some of the most highly refractory conditions, including treatment resistant depression (Andersen et al., 2021; Belouin & Henningfield, 2018; Carhart-Harris et al., 2016; Carhart-Harris & Goodwin, 2017; Goodwin et al., 2022), and substance use disorders (Bogenschutz et al., 2015; Bogenschutz et al., 2022; Garcia-Romeu et al., 2014; Johnson et al., 2014). The studies conducted to date demonstrate that

psychedelic drugs, like psilocybin, which is the active ingredient in so called “magic mushrooms”, do have significant therapeutic value, and do not have a high addictive potential (Johnson et al., 2018).

Psychedelics’ Mechanisms of Action

Psychedelics produce altered states of consciousness that are characterized by profound changes in perception, mood, cognition, and a sense of being a “self” (Nichols, 2016; Swanson, 2018). Converging research from both animal models and human studies has elucidated that at the biological level, psychedelics exert their subjective effects primarily via agonism of a particular serotonin receptor, specifically the 5-HT2A receptor (Dos Santos et al., 2021; Glennon et al., 1984; González-Maeso et al., 2007; Halberstadt, 2015; Madsen et al., 2019; Vollenweider et al., 1998).

5-HT2A receptors are most densely expressed in the evolutionarily new cerebral cortex, particularly the prefrontal cortex, the posterior cingulate cortex, as well as in subcortical regions such as the hippocampus and the amygdala (Dos Santos et al., 2021; López-Giménez & González-Maeso, 2018). Activation of the 5-HT2A receptor (by psychedelics) in those brain structures, which broadly speaking are involved in cognition, learning, memory, and emotional processing (Zhang & Stackman, 2015) induces glutamate release, and increases brain-derived neurotrophic factor (BDNF) expression in the prefrontal cortex (Dos Santos et al., 2021; Mason et al., 2020). BDNF is a key protein involved in learning and memory. In the adult brain, BDNF is known to support the survival of existing neurons as well as encouraging growth of new neurons and synapses (Acheson et al., 1995). Given this, BDNF has important implications for neuroplasticity (Dos Santos et al., 2021).

Ly et al (2018) found that activation of the 5-HT2A receptor by the psychedelic lysergic acid diethylamide (LSD) and other psychedelics induced BDNF, which resulted in cortical synaptogenesis, an important biomarker of neuroplasticity. This is of important potential clinical relevance given that atrophy of neurons in the prefrontal cortex have been suggested to play a key role in the development of various hard-to-treat psychiatric conditions such as major depressive disorder. As such, psychedelic-induced glutamate release leading to increases in BDNF, via activation of the 5-HT2A receptor and the consequent neuroplastic changes that ensue, is currently thought to be one of the main biological mechanisms by which psychedelics confer therapeutic benefits that outlast their acute presence in the body post-dosing (Ly et al., 2018). Based on these findings, some psychedelic researchers are actually proposing a new term to refer to psychedelics*: "psychoplastogens*" (a drug capable of rapidly promoting structural and functional neural plasticity) (Ly et al., 2018; Olson, 2018; Vargas et al., 2021).

Theoretical conceptualizations regarding psychedelics' psychological mechanisms of action are not yet fully developed, and this is an area of ongoing scientific inquiry (Belser et al., 2017). Research from the 1950s, along with modern research conducted since 2006 (Garcia-Romeu et al., 2014; Griffiths et al., 2008; Griffiths et al., 2016; Griffiths et al., 2018; Griffiths et al., 2011; Griffiths et al., 2006; Ross et al., 2016), has consistently identified the elicitation of mystical experiences as a key predictor of both short and long-term therapeutic effects. Additionally, recent findings have also highlighted the importance of psychological flexibility and psychological insight in explaining the psychological mechanisms and therapeutic effects of psychedelics (Agin-Liebes et al., 2022; Davis, Averill, et al., 2020; Davis, Barrett, et al., 2020; Davis, Xin, et al., 2021; Mangini et al., 2022).

Psychological flexibility refers to a set of interconnected processes that enable individuals to recognize and adapt to diverse situational demands. It involves the ability to shift mindsets or behavioral patterns to enhance social functioning and mental well-being. This adaptive capacity allows people to navigate life's challenges more effectively, aligning their actions with personal values and contextual requirements (Gloster et al., 2020; Kashdan & Rottenberg, 2010).

Bridging the biological and psychological mechanisms, it is plausible that the neuroplastic changes elicited by increases in BDNF via 5-HT2A receptor activation would map out to changes in psychological flexibility, and that this would correspond with long-term therapeutic effects in a variety of mental health conditions. This would further hint at the value of psychedelics as transdiagnostic treatment tools (Kočárová et al., 2021), and increases in psychological flexibility could be seen as a unifying underlying psychological mechanism by which psychedelics produce therapeutic effects (Davis, Barrett, et al., 2020; Watts & Luoma, 2020).

To help contextualize the relevance and significance of psychedelic agents as emerging mental health treatments, a brief summary of psilocybin research findings is presented in the next section. Following that, I will offer a brief overview of findings from naturalistic and observational studies regarding the short-acting psychedelic 5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) before I describe the three manuscripts that make up the present dissertation project.

Review of the Literature

To date, the majority of psychedelic research has been conducted using psilocybin, a naturally occurring psychedelic substance found in various mushroom species (Geiger et al.,

2018), and studies to date have shown it provides therapeutic benefit in the treatment of alcohol-use disorder (Bogenschutz et al., 2015; Bogenschutz et al., 2022), smoking cessation (Johnson et al., 2014), anxiety and depression related to an illness (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), major depressive disorder (Davis, Barrett, May, et al., 2021), and treatment-resistant depression (Carhart-Harris et al., 2016; Goodwin et al., 2022). Long-term follow up studies have demonstrated that these positive effects are enduring up to one year later in some cases (Agin-Liebes et al., 2020; Carhart-Harris, Bolstridge, et al., 2018; Johnson et al., 2017).

A recent randomized, wait-list controlled clinical trial that was carried out at Johns Hopkins University and which aimed to examine the therapeutic effects of psilocybin on major depressive disorder found that psilocybin produced rapid and sustained antidepressant effects, with 71% of participants showing a clinically significant response ($\geq$ 50% reduction in depression score as measured by the GRID-HAMD) and 54% of participants showing remission scores ($\leq$7 GRID-HAMD score) at the four-week primary outcome follow-up assessment (Davis, Barrett, May, et al., 2021).

A 12-month follow-up study with this sample showed that response and remission rates remained high throughout the follow-up assessment time points (1, 3, 6, and 12 months), with reported final response and remission rates of 75% and 58% respectively, and a large effect size (Cohen's d = 2.4). This further demonstrates that the substantial antidepressant effects of psilocybin-assisted therapy can be long-lasting with only two doses of psilocybin-assisted therapy (Gukasyan et al., 2022).

In a first-of-its-kind study, a double-blind, randomized, controlled trial conducted at Imperial College London involving patients with major depressive disorder, informed in part by an earlier open label feasibility study (Carhart-Harris et al., 2016), psilocybin was compared to

escitalopram, a commonly used first-line antidepressant medication. Psilocybin was found to reduce depressive symptoms at least as well as escitalopram on the primary outcome measure, but data included in the supplementary materials showed that psilocybin outperformed escitalopram on measures of well-being and flourishing, with only two doses of psilocybin as opposed to six weeks of daily doses of the leading antidepressant medication (Carhart-Harris et al., 2021). Additionally, three recently published randomized, double-blind, placebo-controlled trials showed that a single psilocybin dose produced therapeutic effects in treatment-resistant depression (Goodwin et al., 2022), and major depressive disorder (Von Rotz et al., 2023; Raison et al., 2023).

Along with these findings, qualitative research has shown that psychedelics foster a general sense of connection – to self, others, and the world. Watts et al. (2017) using a thematic analysis of semi-structured interviews identified two main processes of change facilitated by psilocybin: 1) a change from disconnection to connection (to self, others, world); and 2) a change from avoidance to acceptance (of negative emotions). Watts and colleagues articulate that psilocybin therapy seemed to enhance patients' sense of a "shared humanity."

This trend of feelings of interconnectedness or "relational embeddedness" (Belser et al., 2017) is also echoed in other qualitative reports of psychedelic research in end-of-life distress (Belser et al., 2017), and in smoking cessation trials (Noorani et al., 2018). These qualitative studies have also found that profound feelings of awe, and an enhanced capacity for perceiving beauty in the natural world are associated with mystical-type and ego-dissolution experiences (Belser et al., 2017; Noorani et al., 2018; Watts et al., 2017). In turn, experiences of awe in response to psychedelic use have been found to promote increases in nature relatedness (Kettner

et al., 2019; Lyons & Carhart-Harris, 2018; Sagioglou & Forstmann, 2022) and prosocial behaviors (Gandy, 2019; Gandy et al., 2020; Griffiths et al., 2018).

The construct of nature relatedness captures people's perceived sense of connectedness with the natural world (Nisbet & Zelenski, 2013). Increases in nature relatedness have been observed both in clinical research contexts and naturalistic studies with psilocybin (Forstmann et al., 2023; Forstmann & Sagioglou, 2017; Kettner et al., 2019; Lyons & Carhart-Harris, 2018; Watts et al., 2017), and these increases have been associated with increases in psychological well-being (Kettner et al., 2019).

Statement of the Problem

As encouraging as these findings have been, there are rising concerns related to the future viability of psilocybin therapy as a scalable and equitably accessible treatment. A challenge facing the future clinical uptake of psilocybin is the amount of time and resources a well conducted therapy session entails (Davis et al., 2018). The psychedelic experience engendered by psilocybin can last up to eight hours, and two trained clinicians are required to supervise the dosing session. This has been posited to potentially represent a logistical and financial roadblock to making this type of therapy available in an affordable way, particularly for underserved populations, who may in fact be the ones that need this type of therapy most, thus highlighting the need to identify alternative options that could elicit a shorter acute psychedelic effect, while maintaining comparable long-term therapeutic benefits (Ortiz Bernal et al., 2022).

Introducing 5-MeO-DMT

One short-acting psychedelic that has been identified as a potential candidate to circumvent the challenges of psilocybin therapy implementation at scale is 5-Methoxy-*N*,*N*-dimethyltryptamine (referred to as 5-MeO-DMT hereafter). 5-MeO-DMT is a non-selective

serotonin agonist with high affinity for the 5HT1A receptor, and less affinity for the 5-HT2A and 5-HT2C receptor subtypes (Dakic et al., 2017; Szabo et al., 2014).

Known to naturally occur in a variety of South American plant species (e.g., *Anadenanthera peregrina, Virola theiodora*) that were used in snuff preparations by Indigenous tribes such as the Taíno and Yanomamo (Furst, 1976; Torres & Repke, 2006), 5-MeO-DMT has also been found in the skin glands of the *Incilius alvarius* toad. Formerly known by the scientific name *Bufo alvarius*, this toad is the largest amphibian in North America (Rorabaugh & Lemos-Espinal, 2016), and it is endemic to the Sonoran Desert bioregion in northwestern Mexico and southwestern United States, hence its common name "Sonoran Desert toad" (Uthaug et al., 2019; Weil & Davis, 1994).

Interestingly, despite the fact that 5-MeO-DMT is a tryptamine drug, and could have been placed under Schedule 1 classification when the Controlled Substances Act was introduced in 1970, it was actually unscheduled until 2011. This fact points to 5-MeO-DMT's relative obscurity and lack of popularity until fairly recently. Over the past decade, use of 5-MeO-DMT, particularly from toad derived sources, has become increasingly popular, and some data related to its use has been captured in various naturalistic (i.e., use in non-clinical research settings) and observational studies (Barsuglia et al., 2018; Davis et al., 2018; Davis et al., 2019; Lancelotta & Davis, 2020; Sepeda et al., 2020; Uthaug et al., 2019).

5-MeO-DMT Naturalistic and Observational Studies Overview

5-MeO-DMT induces a much shorter altered-state experience than most other psychedelic agents, on the order of 20 to 60 minutes depending on the route of administration, as opposed to six to eight hours for psilocybin (Reckweg et al., 2022; Shen et al., 2010; Uthaug et al., 2020). Of note, despite the significantly reduced period of acute psychedelic effects compared to psilocybin, a low to moderate dose of 5-MeO-DMT reliably induced a mystical

experience of similar intensity to a high-dose of psilocybin administered in clinical settings (Barsuglia et al., 2018). This is of therapeutic significance given that as noted above, the occurrence of mystical experiences has been consistently associated with positive long-term therapeutic outcomes (Garcia-Romeu et al., 2014; Griffiths et al., 2008; Griffiths et al., 2016; Griffiths et al., 2018; Griffiths et al., 2011; Johnson et al., 2017).

Survey studies have found significant symptom improvements across a range of diagnoses including anxiety, depression, substance misuse, and PTSD, with most users engaging in infrequent use primarily for spiritual exploration, and demonstrating low addiction potential (Davis et al., 2018; Davis et al., 2019).

A longitudinal observational study, designed to gather preliminary data on 5-MeO-DMT's effects on mental health variables yielded promising results. Participants reported significant increases in life satisfaction and well-being 24 hours after a single dose of 5-MeO-DMT, with these improvements persisting at the four-week follow-up. Moreover, ratings of depression and anxiety showed significant decreases 24 hours post-dosing, and these reductions remained significant at the four-week mark. These findings suggest potential fast and lasting positive effects of 5-MeO-DMT on mental health outcomes (Uthaug et al., 2019). Two observational studies found significant reductions in symptoms of PTSD and alcohol misuse among United States Veterans who received 5-MeO-DMT as part of a treatment protocol in a clinical setting in México (Davis, Averill, et al., 2020; Mangini et al., 2022). A common finding across both studies was that symptom reductions were associated with increases in psychological flexibility. As noted above, psychological flexibility refers to the ability to adapt one’s mindset and behavior to align with personal values, enhancing social functioning and well-being.

An open-label study assessing the treatment protocol administered in the Mexico clinical setting mentioned above recently showed that there were large and significant improvements in self-reported PTSD symptoms, as well as decreases in depression, anxiety, insomnia severity. The study also reported increases in self-reported satisfaction with life and psychological flexibility (Davis, Xin, et al., 2023). Taken together, this research suggests that 5-MeO-DMT may have transdiagnostic therapeutic potential, demonstrating significant improvements in mental health outcomes across a range of conditions, which appear to be underpinned by increases in psychological flexibility.

The Present Dissertation

Aims

Informed by the studies summarized above, the present three-paper dissertation aimed to explore possible psychological mechanisms and processes that may underlie and partially explain the therapeutic effects that have been documented in relationship to 5-MeO-DMT use (Chapter 2).

Additionally, the dissertation aims to expand previous research that investigated prevalence rates and predictors of a phenomenon associated with the use of 5-MeO-DMT known as reactivation (Ortiz Bernal et al., 2022) (Chapter 3).

Lastly, given the growing popularity of 5-MeO-DMT use and the complex historical and cultural contexts surrounding its various sources, including the *Incilius alvarius* toad, a third aim of this dissertation was to provide a comprehensive historical and cultural examination of 5-MeO-DMT use in ancient and modern times (Chapter 4).

Introduction to the Manuscripts

Manuscript 1

Emerging scientific literature is pointing towards the role of changes in psychological flexibility as both a predictor, and a mediator of psychedelic effects and therapeutic outcomes (Agin-Liebes et al., 2022; Davis, Averill, et al., 2020; Davis, Barrett, et al., 2020; Davis, Xin, et al., 2021; Mangini et al., 2022). Psychological flexibility derives from a therapy model called *Acceptance and Commitment Therapy* (ACT) that been found to be effective across a broad range of psychiatric conditions (Gloster et al., 2020), and it is increasingly being used as part of a supportive framework in psychedelic therapy studies (Luoma, Davis, et al., 2020; Luoma et al., 2019; Sloshower et al., 2020; Watts & Luoma, 2020).

In ACT, distancing from thoughts is known as *cognitive defusion* and it is one of six overlapping processes that make up the therapeutic approach. These six processes (see figure 1) are theorized to lead to psychological flexibility.

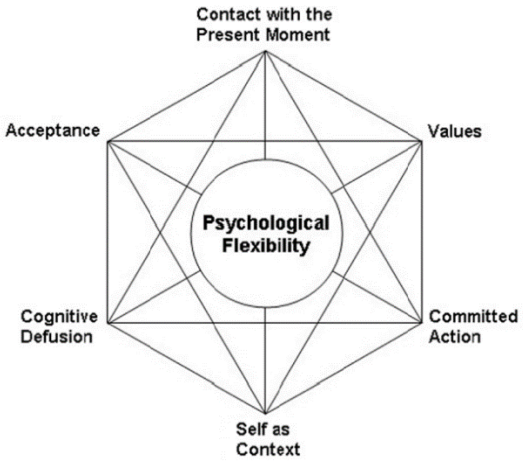

Figure 1: Psychological flexibility model as depicted in Watts and Luoma, 2020.

The opposite to cognitive defusion, *cognitive fusion*, involves becoming entangled in one's thinking patterns to the extent that separation from thoughts becomes difficult. This entanglement with thoughts can lead to significant distress and promote experiential avoidance. Such avoidance behaviors are associated with challenges in social functioning and can contribute

to mental health issues such as a depression and anxiety (Gillanders et al., 2014). Within ACT, fusion is recognized as the overarching pathological process underlying mental health concerns (Harris, 2019).

Based on the psychedelic research findings to date showing that increases in psychological flexibility are associated with mental health improvements (Agin-Liebes et al., 2022; Davis, Averill, et al., 2020; Davis, Barrett, et al., 2020; Davis, Xin, et al., 2023; Davis, Xin, et al., 2021; Mangini et al., 2022), and considering the centrality of cognitive defusion strategies (i.e., to decrease cognitive fusion) as essential for cultivating psychological flexibility within the ACT model (Harris, 2019), I conducted ordinary least squares hierarchical regression analyses in Manuscript 1. These analyses explored the relationships between 5-MeO-DMT use characteristics and acute effects, and retrospective pre-post changes in self-reported cognitive fusion levels.

Additionally, drawing on previous studies showing increases in nature relatedness as a result of psychedelic use (Forstmann et al., 2023; Forstmann & Sagioglou, 2017; Kettner et al., 2019; Lyons & Carhart-Harris, 2018; Watts et al., 2017), and the qualitative evidence around the sense of connection to other humans and the world (Belser et al., 2017; Watts et al., 2017), in manuscript 1 I sought to examine if 5-MeO-DMT, with its significantly shorter duration of acute effects may produce similar pre-post changes in nature relatedness and prosocial behavioral intentions. Lastly, I wanted to explore if changes in the psychological constructs of cognitive fusion, nature relatedness, and prosocial behavioral intentions from before-to-after 5-MeO-DMT use would be associated with positive enduring changes (persisting effects) attributed to the 5-MeO-DMT experience. Specifically, the research questions informing Manuscript 1 were:

1. Is 5-MeO-DMT use in non-clinical settings associated with changes in cognitive fusion, nature relatedness, and prosocial behavioral intentions from before-to-after 5-MeO-DMT use?
2. Is the intensity of 5-MeO-DMT's acute psychedelic effects, as measured by the Ego-Dissolution Inventory, the Challenging Experiences Questionnaire and the Psychological Insight Questionnaire associated with changes in cognitive fusion, nature relatedness and prosocial behavioral intentions?
3. Are positive enduring changes attributed to the 5-MeO-DMT experience, as measured by a set of items from the Persisting Effects Questionnaire associated with changes in cognitive fusion, nature relatedness, and prosocial behavioral intentions?

Manuscript 2

Previous research among two subsamples of English-speaking individuals began an exploration of a phenomenon known to occur in association with 5-MeO-DMT use called reactivation (Ortiz Bernal et al., 2022). The term reactivation is similar to the 1960s term "flashback", which was broadly defined as "a reexperiencing of the drug induced state *after* the drug's effects have worn off and a relative period of normalcy has been experienced"(Heaton & Victor, 1976; Matefy & Krall, 1974). In this sense, reactivations refer to transient aftereffects that may occur days, weeks, sometimes even months after a 5-MeO-DMT dose, during which a person feels they are reexperiencing some felt-sense of their acute 5-MeO-DMT experience.

Manuscript 2 of the present dissertation builds upon the existing research on reactivations by employing logistic regression analyses to explore predictors and emotional responses associated with incidence of the phenomenon among Spanish-speaking individuals. The study also investigates the association between reactivations and factors that may predict the likelihood

of its occurrence. This is valuable work that may contribute to better characterizing the reactivation phenomenon, and broaden naturalistic research on 5-MeO-DMT to include non-English speaking populations. Such inclusivity aims to foster diversity in psychedelic studies and improve their applicability across different cultural contexts. The research questions guiding Manuscript 2 were as follows:

1. What is the prevalence rate of reactivation events associated with the use of 5-MeO-DMT in non-clinical settings among a sample of Spanish-speaking individuals?
2. What are some of the factors that predict the reactivation phenomenon among this sample?
3. What is the self-reported emotional valence of reactivation events and what factors are associated with experiencing reactivations as positive vs neutral or negative.

Manuscript 3

Manuscript 3 explores the historical use of plant-based 5-MeO-DMT sources among Indigenous tribes in South America, examines the significance of a toad motif in Mesoamerican cultures, and addresses contemporary uses of 5-MeO-DMT in North America and around the world. By presenting this historical-cultural perspective, the paper aims to clarify misconceptions about 5-MeO-DMT use, particularly in relation to claims of traditional use by Indigenous tribes in Sonora. Furthermore, it seeks to raise awareness about the conservation challenges facing the Sonoran Desert toad, given the anthropogenic pressures facing the species as a result of the worldwide demand for its 5-MeO-DMT-containing secretions. The research questions guiding Manuscript 3 were:

1. How did Indigenous tribes in South America historically utilize plant-based sources of 5-MeO-DMT?

2. What are the historical and cultural contexts surrounding the toad motif in Mesoamerican cultures, and how has this motif been interpreted over time?
3. What are the contemporary uses and implications of 5-MeO-DMT in North America and globally, and how do these uses align with or differ from traditional indigenous practices as claimed?

Connecting it all

The unifying thread across the three Manuscripts is 5-MeO-DMT. Manuscript 1 (Chapter 2) offers preliminary evidence suggesting potential mechanisms underlying the increased psychological flexibility observed in previous studies, which correlates with symptom improvements across various psychiatric disorders. Manuscript 2 (Chapter 3) addresses the phenomenon of reactivation associated with 5-MeO-DMT use. As controlled clinical trials with 5-MeO-DMT rapidly progress in Europe and the United States, the limited understanding of this complex phenomenon could pose regulatory barriers. This study expands on prior work, demonstrating that reactivations are predominantly experienced positively and do not typically threaten users' well-being. Manuscript 3 (Chapter 4) provides a comprehensive historical and cultural examination of 5-MeO-DMT use, from ancient practices to modern applications. By exploring the historical use of plant-based sources, the significance of a toad motif in Mesoamerican cultures, and contemporary global uses, this paper offers crucial context for understanding the current therapeutic interest in 5-MeO-DMT, and addresses the pressing ecological concerns surrounding the Sonoran Desert toad.

Lastly, in Chapter 5, the dissertation offers some conclusions and outlines possible future directions for clinical investigations into the therapeutic potential of 5-MeO-DMT. It also addresses ethical considerations surrounding the Sonoran Desert toad.

Focus on Spanish-Speaking Populations

It is important to note that despite the growing interest and research with psychedelic substances, there is a striking lack of diversity in study samples, both in clinical trials, and in naturalistic survey studies, with the majority of research being conducted on English-speaking, predominantly White participants (Michaels et al., 2018). This dissertation addresses this gap by focusing on Spanish-speaking populations. Spanish is one of the most spoken languages globally (Eberhard, Simons and Fenning, 2019), and several Spanish-speaking countries in Central and South America have rich traditions of Indigenous psychedelic use dating back thousands of years (Furst, 1976). By including Spanish-speaking participants, this research aims to broaden the cultural applicability of psychedelic studies and ensure that findings are relevant and beneficial to a more diverse group of people. Moreover, understanding the experiences of Spanish-speaking individuals with 5-MeO-DMT can provide valuable insights into how cultural and linguistic factors may influence the therapeutic outcomes of psychedelic use. Thus, this dissertation contributes to the growing body of knowledge by highlighting the importance of diversity and inclusion in psychedelic research, ensuring that the potential benefits of these substances are accessible to a wider population.

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Chapter 2 - Exploring the Associations Between 5-MeO-DMT Use and Changes in Cognitive Fusion, Nature Relatedness, and Prosocial Behavioral Intentions

Abstract

The psychedelic 5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) has shown clinical potential due to its short duration of acute effects and ability to reliably induce ego-dissolution experiences. The psychological mechanisms underlying 5-MeO-DMT's therapeutic effects are not fully known and warranted further study. To explore possible psychological mechanisms, the associations between 5-MeO-DMT use and changes in cognitive fusion, nature relatedness, and prosocial behavioral intentions, as well as 5-MeO-DMT use characteristics were assessed. We also investigated if the intensity of acute effects was associated with changes in those three constructs, and whether they would predict persisting positive changes that were attributed to the 5-MeO-DMT experience.

A cross-sectional survey study was conducted. Descriptive statistics, *t*-tests, Wilcoxon signed rank tests, and hierarchical (nested) multiple regression analyses were employed to explore hypotheses. Results showed challenging experiences and psychological insight predicted decreases in cognitive fusion. Challenging experiences predicted increases in prosocial behavioral intentions. There was no association between increases in nature relatedness and acute effects, and only ego-dissolution effects predicted persisting positive changes. Decreases in cognitive fusion were also associated with the positive persisting changes respondents attributed to the 5-MeO-DMT experience. These findings, although preliminary, suggest that decreases in cognitive fusion may be part of a central mechanism that contributes to 5-MeO-DMT's transdiagnostic therapeutic value, and is a construct that merits further investigation in future 5-MeO-DMT studies.

Keywords: 5-MeO-DMT, cognitive fusion, nature relatedness, prosocial behavioral intentions, ego-dissolution, challenging experiences, psychological insight, persisting effects.

The Current Study

In recent years, research with psilocybin, a classic psychedelic substance that is present in some mushroom species (e.g., *Psilocybe cubensis),* has advanced significantly (Geiger et al., 2018). Numerous studies have demonstrated its safety and efficacy for various psychiatric disorders, including depression, anxiety, and substance use (Bogenschutz et al., 2015; Bogenschutz et al., 2022; Carhart-Harris et al., 2021; Carhart-Harris et al., 2016; Davis, Barrett, May, et al., 2021; Garcia-Romeu et al., 2014; Griffiths et al., 2016; Johnson et al., 2014; Raison et al., 2023; Ross et al., 2016).

At the same time, interest in the potential therapeutic applications of other novel psychedelic substances, such as 5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), has grown rapidly (Kargbo, 2021; Reckweg et al., 2022). 5-MeO-DMT is a naturally occurring psychedelic substance that is present in various South American plants (e.g., *Virola theiodora*, *Anadenanthera peregrina)* (Furst, 1976; Torres & Repke, 2006), and in the defense secretions of the *Incilius alvarius* toad, an amphibian endemic to the Sonoran Desert bioregion in Northwestern Mexico/Southwestern United States (Ermakova et al., 2022; Uthaug et al., 2019; Weil & Davis, 1994). It has also been synthesized in laboratory settings (Morris, 2021; Sherwood et al., 2020), and various synthetic formulations (i.e., intranasal, intramuscular) are currently being investigated as potentially efficacious treatments for several psychiatric conditions (Reckweg et al., 2022), including treatment-resistant depression (Clinical.Trials.gov Identifier: NCT05800860) and postpartum depression (Clinical.Trials.gov Identifier: NCT05804708).

Potential Psychological Mechanisms of Psychedelics' Therapeutic Effects

Although theoretical conceptualizations regarding the psychological mechanisms of psychedelics' therapeutic action are not yet fully developed (Agin-Liebes et al., 2021; Belser et al., 2017), some studies suggest that the intensity of certain acute psychedelic effects is associated with beneficial outcomes (Davis, Barrett, et al., 2020; Davis, Barrett, May, et al., 2021; Garcia-Romeu et al., 2020; Garcia-Romeu et al., 2019). For example, greater ratings of ego-dissolution experiences during the acute psychedelic experience have been associated with greater satisfaction with life, lower depression scores, and enhanced mindfulness-related capacities (Uthaug et al., 2019; Uthaug et al., 2018), as well as increased nature relatedness (Kettner et al., 2019), post-dosing.

The construct of nature relatedness capture's individuals' perceived sense of connectedness with the natural world (Nisbet & Zelenski, 2013). Increases in nature relatedness have been observed in both clinical research and large population-based studies of naturalistic (i.e., non-laboratory) psychedelic use (Forstmann et al., 2023; Forstmann & Sagioglou, 2017; Lyons & Carhart-Harris, 2018; Watts et al., 2017). These increases are associated with enhanced psychological well-being (Gandy et al., 2020; Kettner et al., 2019). Along with increased nature relatedness, psychedelics seem to foster a general sense of connection to self, world and others, enhancing a sense of a "shared humanity"(Watts et al., 2017). Additionally, experiences of awe in response to psychedelic use have been found to promote prosocial behaviors (Gandy, 2019; Griffiths et al., 2018; Hendricks, 2018; Noorani et al., 2018).

Interestingly, although it may seem counterintuitive, difficult and emotionally or physically challenging experiences linked to psychedelic use have been correlated with long-lasting improvements in well-being. Carbonaro et al. (2016) found that over 80% of respondents

reported benefits from these challenging experiences, and 76% noted an increase in life satisfaction attributable to their experiences. This suggests that even difficult experiences with psychedelics may lead to positive outcomes in the long term (Carbonaro et al., 2016).

Moreover, psychological insight is emerging as a robust predictor of psychedelics' therapeutic effects, specifically, decreases in depression and anxiety (Agin-Liebes et al., 2021; Davis, Barrett, et al., 2020; Davis, Barrett, May, et al., 2021), racial trauma symptoms (Davis, Xin, et al., 2021), post-traumatic stress disorder (PTSD) symptoms (Agin-Liebes et al., 2021), and substance misuse (Garcia-Romeu et al., 2020; Garcia-Romeu et al., 2019). This indicates that insight may be an important contributor to the psychological mechanisms underpinning psychedelics' positive mental health effects.

5-MeO-DMT: Subjective Effects and Emerging Research

The acute subjective effects of 5-MeO-DMT have been described as involving a profound ego-dissolution experience, along with an increased range of emotions from awe to terror (Ermakova et al., 2022), and somatic release effects (e.g., shaking, relief of physical tension, symmetrical body movements) (Uthaug et al., 2020).

The experience of ego-dissolution has been described as "a disruption of ego-boundaries, which results in a blurring of the distinction between self-representation and object-representation" (Kałużna et al., 2022; Nour et al., 2016), as well as a "complete loss of subjective self-identity" (Johnson et al., 2008). In ego-dissolution experiences, the ordinary sense of self is replaced by a sense of union with ultimate reality (Letheby & Gerrans, 2017), and this noetic quality is thought to be central to the positive psychological changes and therapeutic effects that may follow a psychedelic experience (Kałużna et al., 2022; Stoliker et al., 2022).

Compared to other psychedelics, 5-MeO-DMT elicits a much shorter altered-state experience, lasting 20-60 minutes depending on the route of administration (Reckweg et al., 2022; Shen et al., 2010). This significantly reduced duration of acute effects has been posited to represent a potential advantage in the process of scaling accessibility to psychedelic treatments (Davis et al., 2019). The shorter experience could facilitate more efficient clinical protocols, potentially allowing for increased patient throughput and reduced resource requirements in therapeutic settings.

Although placebo-controlled studies with 5-MeO-DMT are in the early stages of implementation, and to date only three clinical studies assessing safety, tolerability, and potential antidepressant effect have been published (Reckweg et al., 2021; Reckweg et al., 2023; Rucker et al., 2024), several naturalistic and observational studies provide preliminary evidence suggesting that 5-MeO-DMT may have an adequate safety profile, and hold therapeutic value for treating various psychiatric disorders (Davis et al., 2018; Davis et al., 2019; Uthaug et al., 2019).

Observational Studies and the Role of Context

A naturalistic study that compared acute and enduring effects of synthetic 5-MeO-DMT between individuals who used 5-MeO-DMT in a structured context versus a non-structured context found that both samples reported high ratings on measures of acute effects, and positive persisting effects related to meaningfulness and well-being that respondents attributed to the 5-MeO-DMT experience, but these ratings were significantly higher in the structured context sample (Sepeda et al., 2020). This speaks to the importance of a safe and supportive context for the administration of 5-MeO-DMT in order to optimize beneficial outcomes long-term and minimize any potential adverse effects.

Indeed, context of use has been shown to consistently impact psychedelic use outcomes (Carhart-Harris, Roseman, et al., 2018), so much so that it has become reified through the ubiquitous phrase and concept of "*set and setting*" in psychedelic research (Hartogsohn, 2016). Setting encompasses the context of use, and set refers to a person's internal landscape, including their motivation for using psychedelics. Motivation for using psychedelics has been shown to vary among ethnic groups (Rigg, 2017), and predict different outcomes accordingly (Neitzke-Spruill, 2019). For example, motivations for using 3,4 - Methylenedioxymethamphetamine (MDMA) have been found to differ between African American and White communities. African Americans report using MDMA for sexual enhancement and to alter the effects of other drugs like marijuana and alcohol, whereas White users frequently report using it for introspection, or enhancement of music (Rigg, 2017). Among a sample of English-speaking individuals who used 5-MeO-DMT, 68% of respondents indicated their motivation for using was spiritual exploration (Davis et al., 2018). In a subset of respondents who used synthetic 5-MeO-DMT in a structured ceremonial context, 80% reported unintended improvements in symptoms of depression and anxiety (Davis et al., 2019).

Two observational studies in which 5-MeO-DMT was administered to patients with severe PTSD within a structured therapeutic context showed there were significant increases in psychological flexibility from before-to-after psychedelic treatment, and those increases in psychological flexibility correlated with reductions in retrospective reports of suicidal ideation, trauma-related symptoms, depression, anxiety, and alcohol misuse (Davis, Averill, et al., 2020; Mangini et al., 2022). Psychological flexibility is a transdiagnostic construct that derives from Acceptance and Commitment Therapy (ACT), a therapy model that has shown efficacy across

diagnoses, including in the treatment of anxiety, depression, and substance use disorders (Gloster et al., 2020).

Acceptance and Commitment Therapy as a Supportive Framework for Psychedelic Studies

The ACT model is increasingly used as a supportive framework in psychedelic studies (Luoma, Davis, et al., 2020; Luoma et al., 2019; Sloshower et al., 2020). Within ACT, the goal is to increase psychological flexibility, defined as a set of interrelated processes that enable a person to fully engage with the present moment. Some of these processes include shifting mindsets or behaviors in line with value-driven goals (Gloster et al., 2020; Harris, 2019; Kashdan & Rottenberg, 2010).

Researchers believe this psychological flexibility model could enhance and sustain the therapeutic effects of psychedelics (Luoma, Davis, et al., 2020; Luoma et al., 2019; Sloshower et al., 2020; Watts & Luoma, 2020). For example, it has been proposed that ACT techniques could help participants clarify their values and set intentions during the preparation sessions prior to a psychedelic dosing session, potentially guiding the experience towards desired therapeutic outcomes. Post-dosing sessions, ACT strategies could help individuals process and integrate insights gained during the psychedelic experience, translating them into lasting behavioral changes.

Recent findings support the notion that ACT may be ideally suited for pairing with psychedelic interventions. For example, a study by Davis et al. (2020) showed that increases in psychological flexibility from before-to-after psychedelic use mediated the association between acute psychedelic effects and subsequent decreases in anxiety and depression levels. Similar mediation effects were seen between psychedelic use and improvements in symptoms related to racial trauma (Davis, Xin, et al., 2021). Psychological flexibility was also found to mediate the effects of acute psychological factors on changes in positive mood across various psychiatric

disorders (Agin-Liebes et al., 2022). Taken together these findings suggest ACT processes are relevant in the context of psychedelic therapy and can help account for psychedelics' therapeutic effects.

Cognitive Defusion: A Key Component of Psychological Flexibility

Cognitive defusion, a key concept in ACT, refers to the process of distancing oneself from thoughts. It is one of the six interrelated processes that ACT theorizes lead to psychological flexibility (Hayes et al., 2013). Defusion involves the ability to observe one's thoughts without becoming entangled in them, allowing them to come and go freely (Harris, 2011). Conversely, cognitive fusion occurs when individuals become so enmeshed in their thought patterns that they struggle to differentiate themselves from their thoughts (Gillanders et al., 2014; Gloster et al., 2020; Kashdan & Rottenberg, 2010). Cognitive fusion is considered a transdiagnostic core factor in the development and persistence of many psychiatric disorders (Faustino et al., 2021). Research has shown that cognitive fusion can predict symptoms of anxiety, depression and PTSD (Bardeen & Fergus, 2016; Chen et al., 2023; Thomas & Bardeen, 2020), underscoring its clinical significance.

Aims of the Present Study

Recent studies, including those by Davis et al. (2020) and Mangini et al. (2022) and Davis et al. (2023), have shown that increases in psychological flexibility following 5-MeO-DMT use correlates with reduced symptoms of anxiety, depression, substance misuse, and PTSD. As discussed above, cognitive defusion strategies play a key role in ACT for enhancing psychological flexibility (Gillanders et al., 2014). Building on this connection, the present study examines changes in cognitive fusion levels from before to after 5-MeO-DMT use.

Given that emerging literature suggests psychedelic use is associated with increased feelings of connectedness to self, others, nature (Kałużna et al., 2022; Watts et al., 2022), which are in turn correlated with positive effects and increases in well-being and prosociality (Forstmann et al., 2023; Forstmann & Sagioglou, 2017; Gandy, 2019; Gandy et al., 2020; Griffiths et al., 2018; Lyons & Carhart-Harris, 2018; Watts et al., 2017), additional aims of the study were to explore if 5-MeO-DMT, with its shorter duration of acute effects, may produce positive effects related to changes in nature relatedness and prosocial behavioral intentions that have been observed following administration of other psychedelics that produce longer acute psychedelic experiences. This study hypothesized that there would be significant within-person decreases in cognitive fusion, and significant increases in nature relatedness, and prosocial behavioral intentions from before-to-after 5-MeO-DMT use. We further hypothesized that greater intensity of acute 5-MeO-DMT effects (including ego-dissolution, challenging experiences, and psychological insight) would be associated with larger changes in cognitive fusion, nature relatedness, and prosocial behavioral intentions. Lastly, building on the previous hypotheses, we expected that greater persisting positive changes in overall well-being and life satisfaction attributed to the 5-MeO-DMT experience would be associated with larger decreases in cognitive fusion, and larger increases in nature relatedness and prosocial behavioral intentions.

Cultural and Linguistic Considerations

The present study extends the investigation of 5-MeO-DMT's effects to a Spanish-speaking population, addressing a critical gap in the existing literature. Previous naturalistic survey studies have predominantly focused on English-speaking respondents, which may not fully capture the diversity of experiences and outcomes associated with 5-MeO-DMT use. By focusing on Spanish-speaking individuals, this study aims to explore whether cultural and

linguistic differences influence the psychological mechanisms of therapeutic effects of 5-MeO-DMT. This represents an essential step for developing culturally sensitive therapeutic practices and ensuring the benefit of these emerging treatments are accessible to a broader population.

Method

Measure Translation

All measures included in the study and described below were translated using the forward-and-back translation technique as described previously (Davis et al., 2023). Briefly, translations were performed by team members fluent in English and native Spanish speakers. The survey was initially created in English and then translated into Spanish by a team member. Subsequently, this Spanish version was back-translated into English by another team member. The back-translation was compared to the original English questionnaires to ensure that the translation process had not altered the meaning. In the event of discrepancies or confusion, individual phrases were retranslated to ensure appropriate clarity and meaning. This rigorous translation process aimed to maintain the integrity of the questionnaires and ensure the suitability for Spanish-speaking participants.

Study Procedure and Flow

Data for the present study were collected as part of a larger anonymous online-based cross-sectional survey of Spanish-speaking individuals who reported having used a psychedelic substance at least once. Respondents were asked to complete the survey based on a memorable experience with one of four psychedelic substances: mescaline/Peyote/San Pedro, psilocybin/psilocybin mushrooms, LSD, or 5-MeO-DMT. The present study is limited to the sub-sample of respondents who selected 5-MeO-DMT.

Recruitment took place from June 2020 to June 2021 through online advertisements

posted on relevant websites (e.g., www.drugs-forum.com), email invitations, online flyers, and word of mouth. Interested individuals were referred to an electronic copy of the official survey recruitment flyer. After clicking on the secured survey link (hosted on www.qualtrics.com), each respondent was presented with a statement regarding the purpose of the study, and the informed consent document detailing inclusion criteria (e.g., being at least 18 years old; able to read, write, and speak Spanish fluently; having taken 5-MeO-DMT at least once). After completing the consent document, respondents completed the survey questions based on their most memorable experience with 5-MeO-DMT. A total of 379 people consented to complete the 5-MeO-DMT survey. However, of these, 289 did not begin the survey and were excluded from analyses, yielding a total sample of 90 respondents.

No identifying information was collected. No incentives or compensation were offered. This study was deemed exempt from IRB review at the University of Wisconsin-Madison.

Measures

Demographics. Demographic data captured included current age, age at the time of the 5-Me-O-DMT dose, gender (e.g., male, female), education level (e.g., graduated high school/technical school, some college – no degree, associate's/bachelor's degree, and advanced degree), and country of resident of each respondent.

5-MeO-DMT Use Characteristics. Respondents indicated their motivation for using 5-MeO-DMT (e.g., spiritual exploration, mental health treatment, personal growth/experimentation), location of use (e.g., own or friend's apartment/house, outdoors, church/ceremony/treatment center/other), and the amount of time planned ahead for their 5-MeO-DMT experience (e.g., no plan or a few days, one week or more).

Acute 5-MeO-DMT Effects. Given frequent reports of 5-MeO-DMT's ego-dissolving characteristics (Ermakova et al., 2022; Reckweg et al., 2022), acute psychedelic effects of the 5-MeO-DMT experience were assessed using the Ego-dissolution Inventory (Nour et al., 2016). This is an 8-item self-report scale that assesses the degree to which individuals lose the capacity for self-referential processing during a psychedelic experience. It includes items such as "I experienced a disintegration of my "self" or ego" and "I felt at one with the universe" (Nour et al., 2016). Respondents were asked to think back to their 5-MeO-DMT memorable experience and to rate the intensity with which they experienced each of the items at any point during their experience. The scale is rated using a 6-point Likert scale ranging from 0 = "No; not at all" to 5 = "Extremely." The total score is the mean of the eight items. The higher the total score, the stronger the experience of ego-dissolution. This measure has been found to have high internal consistency and construct validity (Nour et al., 2016). Internal consistency in our sample was good ($\alpha = .89$).

To assess challenging experiences in relation to 5-MeO-DMT use, we included the Challenging Experiences Questionnaire (Barrett et al., 2016). This 26-item questionnaire assesses difficult experiences related to acute psychedelic effects, including feelings of grief, fear, insanity, death, isolation, physical distress, or paranoia. Respondents were asked to think back to their memorable 5-MeO-DMT dose and to rate the intensity with which they experienced each of the items at any point during their experience. Sample items of this scale include *"*I had the profound experience of my own death" and "Feeling my body shake/tremble*."* This scale is scored using a 6-point Likert scale ranging from 0 = "None; not at all" to 5 = "Extremely." Previous studies have found this scale has excellent internal consistency (Davis, Xin, et al., 2021), which was also reflected in our sample ($\alpha = .94$).

Psychological insight effects were measured using the Psychological Insight Questionnaire. This validated 23-item scale was specifically designed to assess insight experiences that may occur in association with psychedelic use. Insight experiences can be related to emotions, beliefs, memories, and relationships (Davis, Barrett, So, et al., 2021). Respondents were asked to think back to their 5-MeO-DMT experience and to rate the degree to which they experienced each of the scale items. Scale items include statements such as "Discovered I could explore uncomfortable or painful feelings I previously avoided" and "Realized how current feelings or perceptions are related to events from my past." The scale is scored using a 6-point Likert-type scale ranging from 0 = "None; not at all" to 5 = "Extremely." Previous studies have found this scale had excellent internal consistency (Davis, Barrett, et al., 2020; Moreton et al., 2022) which was also reflected in the present study ($\alpha = .95$).

Changes in psychological functioning (before and after measures). Cognitive fusion was assessed using the Cognitive Fusion Questionnaire (Gillanders et al., 2014). This is a 7-item scale that assesses excessive attachment to the literal content of thoughts and rigid cognitions. Respondents were asked to indicate to what extent each statement was true for them before and after their 5-MeO-DMT experience. Sample items from this scale are "My thoughts cause me distress or emotional pain" and "I get so caught up in my thoughts that I am unable to do the things that I most want to do." Questions of this scale are recorded on a 7-point scale ranging from 1 = "Never true" to 7 = "Always true." Respondents completed this measure twice: once with respect to before their memorable 5-MeO-DMT experience, and once with respect to after their memorable 5-MeO-DMT experience. Higher scores indicate higher levels of cognitive fusion. Decreases in cognitive fusion indicate psychological improvement. There is good preliminary evidence of the questionnaire's factor structure, reliability, temporal stability,

validity, discriminant validity, and sensitivity to treatment effects (Gillanders et al., 2014). The internal consistency of this scale in our sample was excellent (α = .93 for before and α = .90 for after).

Nature relatedness was measured using the Nature Relatedness Short-Scale (NR-6) (Nisbet & Zelenski, 2013). This is a six-item scale designed to capture one's perceived sense of connectedness with the natural world. Respondents were asked to indicate to what extent each statement was true for them before and after their 5-MeO-DMT experience. Sample items from this scale include statements such as "I am always thinking how my actions affect the environment." Questions are recorded on a 5-point scale ranging from 1 = "Disagree strongly" to 5 = "Agree strongly." Respondents completed this measure twice: once with respect to before their memorable 5-MeO-DMT experience, and once with respect to after. The NR-6 has been found to have good internal consistency, temporal stability, and predictive capacity as a unidimensional scale (Nisbet & Zelenski, 2013). Internal consistency of this scale in our sample was good (α = .90 for before, and α = .89 for after).

Prosocial Behavioral Intentions were examined using the Prosocial Behavioral Intentions Scale (PBIS). This four-item scale was developed to measure prosocial behavioral intentions across different contexts (Baumsteiger & Siegel, 2019). Respondents were asked to indicate to what extent each statement was true for them before and after their 5-MeO-DMT experience. Sample items from this scale include statements such as, "Please indicate to what extent you were likely to engage in any of the following behaviors before/after your 5-MeO-DMT experience… comfort someone I know after they've experienced hardship?" This scale is scored using a 7-point Likert scale ranging from 1 = "I definitely would not do this" to 7 = "I would definitely do this." Total score is calculated by computing the mean of all items. Respondents

completed this measure twice: once with respect to before their memorable 5-MeO-DMT experience, and once with respect to after. The PBIS has been found to be internally consistent, with good convergent validity and incremental predictive validity (Baumsteiger & Siegel, 2019). Internal consistency of this scale in our sample was fair to good ($\alpha = .79$ for before and $\alpha = .87$ for after).

Persisting positive changes related to life satisfaction and well-being attributed to 5-MeO-DMT use were assessed using a set of items from the Persisting Effects Questionnaire that have been used in previous studies (Agin-Liebes et al., 2021; Nikolaidis et al., 2023; Uthaug et al., 2022). These 11 items inquired about the degree to which each respondent believed their 5-MeO-DMT experience, and their contemplation of that experience, had led to persisting long-term changes in their: 1) current sense of well-being and life satisfaction, 2) life's purpose, 3) life's meaning, 4) social relationships, 5) attitudes about life, 6) attitudes about themselves, 7) relationship to nature, 8) behavioral changes, 9) spirituality, 10) attitudes about death, and 11) beliefs about the nature of reality and the universe. These items are scored using a 7-point scale ranging from (-3) = "Strong negative change that I consider undesirable" to 3 = "Strong positive change that I consider desirable." Although these items have been used as stand-alone items in previous studies (Agin-Liebes et al., 2021; Nikolaidis et al., 2023; Uthaug et al., 2022), in the present study all items were highly correlated with each other, and the internal consistency of the items as a sum score was excellent ($\alpha = .97$).

Plan for Analysis

First, descriptive statistics for demographic and background characteristics for all study variables were tabulated. The mean change score in cognitive fusion was determined by subtracting the mean cognitive fusion score before the 5-MeO-DMT experience from the mean

score after the experience for each respondent, following the methodology of previously published studies that have utilized change scores (Davis, Barrett, et al., 2020). The same approach was used to calculate the change scores for nature relatedness and prosocial behavioral intentions. To examine the hypotheses concerning changes in cognitive fusion, nature relatedness, and prosocial behavioral intentions following 5-MeO-DMT administration, two-tailed paired *t*-tests were initially conducted due to their sensitivity in detecting mean differences. A significance level of $p < .05$ was applied to determine statistical significance. Cohen's *d* was utilized to estimate effect sizes, aiding in the interpretation of significant findings.

For non-normally distributed outcome variables, additional analyses were planned using Wilcoxon signed-rank tests. These non-parametric tests provide a more robust confirmation of the results by handling non-normally distributed data more appropriately. Effect sizes for non-parametric tests are to be calculated using the method recommended by Tomczak and Tomczak (2014). Specifically, the rank correlation coefficient (*r*), analogous to Cohen's *d* for parametric tests, is derived from the *z* statistic divided by the square root of the sample size (*n*). This coefficient ranges from -1 to 1, where 0 denotes no association, and higher absolute values indicate stronger effects. Common interpretation values for *r* in the literature are as follows: 0.10 - < 0.3 (small effect), 0.30 - < 0.5 (moderate effect), and >= 0.5 (large effect) (Kassambara, 2023; Tomczak & Tomczak, 2014). To test the set of hypotheses regarding the associations between the intensity of acute psychedelic effects and before-to-after changes in cognitive fusion, nature relatedness and prosocial behavioral intentions, three separate sets of ordinary least squares (OLS) hierarchical regression models were estimated. The change score in cognitive fusion, nature relatedness and prosocial behavioral intentions served as the respective outcome variables, with predictor variables entered in blocks. Block 1 included only age at time

of experience. Block 2 added variables related to 5-MeO-DMT use characteristics. Measures of acute psychedelic effects were included in Block 3, and the change score in cognitive fusion, nature relatedness and prosocial behavioral intentions were added in block 4 of each respective model. A threshold of $p < 0.05$ was used to determine statistical significance. This analytical method facilitated the evaluation of each block's unique contribution, beyond the effects of previously entered variables. Likelihood-ratio tests were conducted to determine if the addition of each new block of variables significantly improved the model fit.

In Block 1 (Model 1) age at the time of the 5-MeO-DMT experience was entered. In Block 2 (Model 2), 5-MeO-DMT use characteristics were added: motivation for using (e.g., spiritual exploration, mental health treatment, personal growth/experimentation), location of use (e.g., own or friend's apartment/house, outdoors, church/ceremony/treatment center/other), and the amount of time planned ahead for a 5-MeO-DMT experience (e.g., no plan or a few days versus one week or more). These categorical variables were entered as dummy-coded variables with the first level of each category acting as the reference category. In Block 3 (Model 3), acute psychedelic effects measures were added: ego-dissolution, challenging experiences, and psychological insight effects.

Predicted change scores were used to interpret the results of regression analyses where the dependent variable was the change score in cognitive fusion, nature relatedness and prosocial behavioral intentions from before-to-after the 5-MeO-DMT experience. Variables were centered, and predicted values for each category of the categorical predictors were calculated while holding other variables at their mean. The differences between these predicted values represent the comparative mean changes, providing a clearer interpretation of the regression results in terms of practical significance. Lastly, to test the set of hypotheses regarding the associations

between persisting positive changes attributed to the 5-MeO-DMT experience and changes in cognitive fusion, nature relatedness and prosocial behavioral intentions, three additional sets of OLS hierarchical regression models were estimated. The outcome variable was a composite score derived from the sum of 11 items from the Persisting Effects Questionnaire included in the study. Predictor variables were the same as those listed in Models 1, 2 and 3 above.

In Block 4 (Model 4), the change scores for cognitive fusion, nature relatedness and prosocial behavioral intentions were added (in three separate models) to assess the associations between persisting positive changes attributed to the 5-MeO-DMT experience, and mean changes in these three constructs.

Given the potential for significant skewness and non-normality in the distribution of the persisting effects composite score variable, which has not been previously reported in the literature, additional analyses were planned using Tobit regression models if these characteristics were confirmed. Tobit regression is appropriate for handling censored data and can provide more reliable estimates under these conditions.

For each of the three associations of interest (i.e., the association between persisting effects and changes in 1) cognitive fusion, 2) nature relatedness, and 3) prosocial behavioral intentions), three Tobit regression models were estimated, with the same predictors entered in blocks as described above for the OLS models. Due to the redundancy in Models 1, 2, and 3, and given the comprehensive inclusion of all predictors in Model 4, only the results for Model 4 are reported for the Tobit analyses. This approach ensures clarity and conciseness in presenting the findings while still accounting for the full set of predictors. Residual diagnostics, including Q-Q plots, would be generated for both OLS and Tobit models to assess the normality of residuals and compare model fits. This comprehensive analysis approach ensures that the findings are

robust and appropriately account for the distributional characteristics of the data, providing a more accurate interpretation of the relations between 5-MeO-DMT use and any potential long-term positive changes.

Results

Descriptive Data

Table 1 displays demographic and 5-MeO-DMT use characteristics of this study's sample. Average age of respondents was 38.89 (*SD* = 11.57), 67% were male, 46% had at least some college education, 35% had an associate or bachelor's degree, and 19% had an advanced degree. Over half indicated México was their country of origin (53%). The other half were from various South American, Central American, as well as European countries, and the United States. The mean age at the time of the 5-MeO-DMT experience was 35.02 (*SD* = 11.93).

The descriptive statistics for the measures of acute effects revealed the following: The mean score for ego-dissolution was 3.86 (*SD* = 1.07; range: 0.62 to 5.00). Challenging experiences had a mean score of 1.16 (*SD* = 0.99; range: 0.00 to 4.66). Psychological insight had a mean score of 2.93 (S*D* = 1.20); range: 3.6 to 5.00).

Before-to-After Changes

Table 2 presents results from the *t*-tests conducted to explore changes in cognitive fusion, nature relatedness and prosocial behavioral intentions from before-to-after 5-MeO-DMT use. Significant within-person decreases in cognitive fusion were observed ($p<.001$; Cohen's $d = -1.25$), supporting the hypothesized direction of this outcome variable. Additionally, results showed significant within-person increases in nature relatedness ($p<0.001$; Cohen's $d = 0.93$), and prosocial behavioral intentions ($p<.001$, Cohen's $d = 0.80$), aligning with the hypothesized direction of change for these variables. Due to the non-normal distribution of these outcomes,

Wilcoxon signed-rank tests were performed as follow-up analyses, confirming that all three change scores remained statistically significant ($p < .001$). The effect sizes for changes in cognitive fusion, nature relatedness, and prosocial behavioral intentions were as follows: $r = -0.85$, $r = 0.80$, and $r = 0.71$, respectively.

Hierarchical Regression Analyses

Cognitive Fusion Regression Analyses. Table 3 shows results examining the associations between predictor variables and changes in the cognitive fusion change score. The demographic variable age at time of 5-MeO-DMT entered in Model 1 was not associated with the outcome. $R^2 = 1\%$.

5-MeO-DMT use characteristic variables (e.g. motivation for use, location of use, time planned ahead) entered in Model 2 contributed an incremental $R^2 = 19\%$. A likelihood ratio test revealed the increase in proportion of variance explained by this set of predictors was statistically significant ($\chi^2 = 19.67$, $p = .001$). Findings suggest, that on average, compared to respondents who used 5-MeO-DMT for spiritual exploration, those who used it for personal growth/experimentation had smaller mean decreases in the cognitive fusion change score ($B = 0.73$, $p = .021$). Specifically, those who used 5-MeO-DMT for spiritual exploration reasons had a decrease of about -1.99 points on average, while those who used it for personal growth/experimentation reasons had a decrease of about -1.26 points, controlling for all other variables in Model 2 as indicated in Table 3.

Compared to respondents who took 5-MeO-DMT in their own apartment/home or a friend's apartment/home, those who took it in a church/ceremony/treatment center/other, on average, had smaller decreases in the cognitive fusion change score ($B = 0.90$, $p = .026$). Specifically, those that took it in their own or a friend's apartment/home had a decrease of about

-1.99, while those that took it in a church/ceremony/treatment setting had a decrease of about -1.09, controlling for all other variables in Model 2 as indicated in Table 3.

Compared to respondents who did not plan or only planned for a few days, those who planned ahead for at least one week or longer had greater decreases in the cognitive fusion change score (B = - 0.81, p =.004). Specifically, those who did not plan/planned for a few days had a decrease of about -1.99, while those who planned ahead for a week or longer, had a decrease of about -2.8 points, controlling for all other variables in Model 2 as indicated in Table 3. Total R^2 in Model 2 = 20%.

The measures of acute 5-MeO-DMT effects (e.g., ego dissolution, challenging and psychological insight) entered in Model 3 contributed an incremental R^2 = 20%. The likelihood ratio test for this Model was significant, indicating a substantial improvement in model fit by this set of predictors, (χ^2 = 25.32, p <.001). Challenging experiences were associated with larger decreases in cognitive fusion (B = - 0.28, p = .030), and psychological insight was also a significant predictor (B = - 0.39, p = .001), while controlling for all other variables in Model 3 as indicated in Table 3.

In Model 3, using 5-MeO-DMT in an outdoors setting emerged as a significant predictor of decreases in cognitive fusion (B = .59, p = .049), suggesting that compared to those that used 5-MeO-DMT at their own or a friend's home/apartment, the ones who used it outdoors had smaller decreases in cognitive fusion. That is, those who used it in their own or a friend's home/apartment had a decrease of about -1.96 points, while those who took it outdoors had a decrease of about -1.37 points, controlling for all variables in the model as indicated in Table 4. Time planned ahead remained a significant predictor in Model 3 (B = -.57, p = .025), which suggests that compared to those that only planned ahead for a few days, those that planned

longer had larger decreases in levels of cognitive fusion. That is, those who did not plan or planned only a few days had a decrease of about -1.96 points, while those who planned for a week or longer had a decrease of about -2.53 points. Total R^2 in Model 3 = 40%.

Nature Relatedness Regression Analyses. Table 4 shows hierarchical regression analyses results examining the associations between predictor variables and changes in the nature relatedness change score. In Model 1, age at time of 5-MeO-DMT dose was not associated with the outcome. R^2 = 0%.

5-MeO-DMT use characteristics added in Model 2 yielded an incremental R^2 = 7%. However, a likelihood ratio test showed this increase in proportion of variance explained was not statistically significant. The only significant predictor of increases in nature relatedness was motivation for using 5-MeO-DMT. Results suggest that, on average, individuals who used 5-MeO-DMT for spiritual exploration reasons experienced larger increases in nature relatedness compared to those who used it for personal growth or experimentation reasons (B = - 0.55. p = .045). Specifically, those who used it for spiritual exploration reasons had an increase in the nature relatedness change score of about 1.10 points, while those that used it for personal growth/experimentation had an increase of about 0.55 points, when controlling for all other variables in Model 2 as indicated in Table 4.

The measures of acute 5-MeO-DMT effects added in Model 3 contributed an incremental R^2 = 3%. However, a likelihood ratio test revealed this increase was not statistically significant. Neither of the acute effects measures were associated with increases in nature relatedness. Total R^2 in Model 3 = 10%.

Prosocial Behavioral Intentions Regression Analyses. Table 5 shows hierarchical regression analyses results examining the associations between predictor variables and changes

in the prosocial behavioral intentions change score. In Model 1, age at time of 5-MeO-DMT experience was not associated with the outcome. $R^2 = 0\%$.

5-MeO-DMT use characteristics added in Model 2 yielded an incremental $R^2 = 12\%$. A likelihood ratio test revealed this increase in proportion of variance explained was statistically significant ($\chi^2 = 11.62$, $p = .040$). Significant predictors were motivation for using 5-MeO-DMT and time planned ahead for the dose. Results suggest that respondents who used 5-MeO-DMT for spiritual exploration had larger mean increases in their prosocial behavioral intentions change score, compared to respondents who used 5-MeO-DMT for personal growth or experimentation ($B = -.47$, $p = .045$). Specifically, those who used it for spiritual exploration purposes had an increase of about 0.70 points, whereas those that used it for personal growth or experimentation had an increase of about 0.23 points when controlling for all other variables in Model 2 as indicated in Table 5. Compared to those who did not plan or only planned for a few days, those who planned ahead at least one week in advance had greater mean increases in the prosocial behavioral intentions change score ($B = .49$, $p = .020$). Specifically, those that did not plan or planned for a few days had an increase of about 0.70 points, while those who planned ahead a week or longer had an increase of about 1.19 points, controlling for all other variables in Model 2 as indicated in Table 6. Total R^2 in Model 2 = 12%.

The measures of acute 5-MeO-DMT effects added in Model 3 contributed an additional $R^2 = 8\%$. The likelihood ratio test revealed this increase was statistically significant ($\chi^2 = 8.70$, $p = .033$). The only significant predictor of increases in the prosocial behavioral intentions change score were the challenging effects ($B = .24$, $p = .021$), which suggests that greater ratings of challenging experiences, on average, were associated with greater increases in prosocial behavioral intentions. Time planned ahead remained a significant predictor of increases in

prosocial behavioral intentions in Model 3 (B = 0.42, p = .047), suggesting that compared to those that didn't plan or planned a few days in advance, those that planned ahead for a week or longer had a larger mean increases in the prosocial behavioral intentions change score. Specifically, those who did not plan or planned only for a few days had an increase of about 0.67 points, while those who planned for a week or more had an increase of about 1.09 points, controlling for all other variables in Model 3 as indicated in Table 6. The total R^2 in Model 3 = 20%.

Associations Between Enduring Positive Changes and Changes Scores

The Shapiro-Wilk test showed that the persisting effects sum score variable used as the dependent variable in the set of analyses examining the relations between persisting effects and the independent variables in Models 1 – 4 was not normally distributed. Furthermore, visual inspection (Q-Q plot) of the final persisting effects regression model residuals (i.e., Model 4 for examining the association between persisting effects and changes in cognitive fusion) showed moderate violations of the normality assumption (See Appendix 1). Similarly, the final models (i.e., Model 4) for nature relatedness and prosocial behavioral intentions described below also showed normality deviation of the residuals (See Appendix 2 and 3 respectively). Given these violations, Tobit regression models were further estimated to address the non-normality and censored nature of the data. Both OLS and Tobit model findings are presented below.

Table 6a shows results of the OLS hierarchical regression analyses examining the associations between persisting positive changes attributed to the 5-MeO-DMT experience and changes in the cognitive fusion change score. In Model 1, age at time of 5-MeO-DMT use was a significant predictor, suggesting that older age is associated with higher persisting positive effects (B = .30, p = .008). For each additional year a participant reported being at the time of 5-

MeO-DMT use, there was an increase, on average, of about 0.30 points in their persisting effects composite score. Model 1 yielded an R^2 = 8%.

5-MeO-DMT use characteristics added in Model 2 contributed an incremental R^2 = 4%. However, a likelihood ratio test revealed this increase was not statistically significant. Total R^2 in Model 2 = 12%.

The measures of acute 5-MeO-DMT effects added in Model 3 contributed an additional R^2 = 16%. The likelihood ratio test showed this increase was statistically significant (X^2 = 18.25, p <.001). Greater ratings of ego-dissolution were strongly associated with greater persisting positive effects (B = 5.46, p <.001). Results suggest that on average, for every one-point increase in the ratings of ego-dissolution, there was an increase of about 5.46 points in the persisting effects composite score. Total R^2 in Model 3 = 28%.

Lastly, in Model 4, changes in cognitive fusion were assessed. This model yielded an incremental R^2 = 4%. The likelihood ratio test showed this increase of proportion of variance explained was statistically significant (χ^2 = 4.77, p = .029). Greater reductions in cognitive fusion were associated with greater persisting positive effects (B = 2.41, p = .041). This finding suggests that for each additional point decrease in the mean change score for cognitive fusion, respondents, on average, reported an increase of approximately 2.41 points in the persisting effects composite score. The total R^2 of Model 4 = 32%.

Table 6b shows results of the Tobit regression model estimated to address the non-normality and skewness of the persisting effects outcome variable distribution, and the consequent non-normal residuals from the OLS model.

As was the case in the OLS model, older age (B = 0.44, p = .001) and greater ratings of ego-dissolution (B = 6.95, p = <.001) were significantly associated with higher scores in the

composite measure of persisting positive effects. Specifically, for each additional year of age, the sum score of persisting effects increases by approximately 0.44 points, considering both the change in value for uncensored observations and the probability of being uncensored.

A significant positive association between motivation for using 5-MeO-DMT and greater ratings of positive persisting effects was found in the Tobit model. Respondents who indicated had used 5-MeO-DMT as a mental health treatment reported significantly higher persisting positive effects compared to those who used it for spiritual exploration ($B = 9.45$, $p = .024$). This finding was not significant in the OLS model but emerged as significant in the Tobit model, suggesting that when accounting for skewness and censored data, the motivation for using 5-MeO-DMT as a mental health treatment becomes an important predictor of long-term positive outcomes. This implies that the Tobit model, by considering both the change in the value for uncensored observations and the probability of being uncensored, provide a more comprehensive understanding of the predictors of persisting effects. The changes in cognitive fusion that were significant in the OLS model, were not significant in the Tobit model.

The model fit statistics for the Tobit regression indicated a good fit: the log likelihood was -287.99, the likelihood ratio chi-square was 38.47, with a p value <.001, and the pseudo R^2 was 0.062.

Associations Between Enduring Positive Changes and Nature Relatedness Increases

Results of the analyses conducted to explore the associations between persisting positive changes attributed to the 5-MeO-DMT experience and nature relatedness change score are shown in Table 7a. Models 1, 2, and 3 are exactly the same as those described in the preceding section.

In Model 4 changes in nature relatedness were assessed. This model did not yield an increase in R^2. Increases in nature relatedness were not a significant predictor of persisting effects. The total R^2 in Model 4 = 28%.

Table 7b shows results of the Tobit regression model examining the associations between changes in persisting positive changes attributed to the 5-MeO-DMT experience and changes in nature relatedness that was estimated to address the non-normal distribution of the residuals from the OLS model. Older age at time of 5-MeO-DMT (B = 0.42, p = .002), using it as a mental health treatment (B = 9.30, p =.030, and greater ego dissolution rating (B = 6.57, p = <.001) were significant predictors. This suggests that for each additional year at the time of 5-MeO-DMT use, there is an increase, on average, of approximately 0.42 points, and for each additional point in the ego-dissolution ratings, there is an increase of about 6.57 points in the persisting effects composite score, when considering both the change in value for uncensored observations and the probability of being uncensored.

Furthermore, respondents who used 5-MeO-DMT as a mental health treatment reported significantly higher persisting effects compared to those who used it for spiritual exploration. This finding, which was not significant in the OLS model, suggests that motivation for using 5-MeO-DMT is a relevant factor in determining long-term positive outcomes when accounting for skewness and censored data. Changes in nature relatedness from before-to-after 5-MeO-DMT use were not associated with higher persisting positive changes.

The model fit statistics for the Tobit regression indicated a good fit: the log likelihood was -288.89, the likelihood ratio chi-square was 36.66, with a p value <.001 and the pseudo R^2 was 0.050.

Associations Between Enduring Positive Changes and Prosocial Behavioral Intentions Increases

Results of the analyses conducted to explore the associations between persisting effects and changes in prosocial behavioral intentions are shown in Table 8a. Models 1, 2, and 3 are exactly the same as described previously. In Model 4 changes in prosocial behavioral intentions were assessed. This model yielded an incremental R^2 = 1%. Increases in prosocial behavioral intentions were not a significant predictor of persisting positive changes. The total R^2 in Model 4 = 29%.

Table 8b shows results of the Tobit regression model examining the associations between persisting positive changes attributed to the 5-MeO-DMT experience and changes in prosocial behavioral intentions. Older age (B = 0.43, p =.001), and ego-dissolution (B = 6.50, p = .<001) were significant predictors of positive persisting effects, suggesting that for each additional year at time of using, there is an increase, on average, of about 0.43 points in the sum score of persisting positive changes. Similarly, for each additional point in the ego-dissolution ratings, there is an increase of about 6.50 points in the sum score of persisting positive changes, when considering both the change in value for uncensored observations and the probability of being uncensored.

Respondents who used 5-MeO-DMT as a mental health treatment reported significantly higher persisting positive effects compared to those who used it for spiritual exploration (B = 9.64, p = .025), when considering both the change in value for uncensored observations and the probability of being uncensored. No significant association between increases in prosocial behavioral changes and positive persisting changes was found.

The model fit statistics for the Tobit regression indicated a good fit: the log likelihood was -294.02, the likelihood ratio chi-square was 37.13, with a p value <.001, and the pseudo R^2 was 0.060.

Discussion

The present retrospective cross-sectional survey study explored possible psychological mechanisms that may underlie the documented therapeutic effects of 5-MeO-DMT. Specifically, we examined changes in the psychological constructs of cognitive fusion, nature relatedness and prosocial behavioral intentions from before-to-after 5-MeO-DMT use among a sample of Spanish-speaking people from México and other countries. As hypothesized, we found significant decreases in cognitive fusion and increases in nature relatedness and prosocial behavioral intentions in both parametric and non-parametric tests.

Our hierarchical regression models revealed that cognitive fusion decreases were associated with challenging experiences and psychological insight, while prosocial behavioral intentions were associated with challenging experiences alone. No associations were found between acute effects and increases in nature relatedness.

Interestingly, ego-dissolution – a state in which the sense of self is temporarily diminished by a marked reduction in self-referential processing – though not associated with changes in cognitive fusion, nature relatedness, or prosocial behavioral intentions, was strongly correlated with persisting positive effects in overall well-being and life satisfaction (e.g., meaning, purpose, attitudes, relationships) that respondents attributed to their 5-MeO-DMT experience. Although the estimates from the OLS models ought to be interpreted with caution, given the violations of normality found in the residuals, this finding was validated using the Tobit model, which addressed these concerns by accounting for skewness and non-normality.

In the OLS model, decreases in cognitive fusion – but not increases in nature relatedness or prosocial behavioral intentions increases – were significantly associated with persisting positive changes. However, in the Tobit model, decreases in cognitive fusion were no longer a significant predictor. This change in significance suggests that while cognitive fusion decreases appear to be important, their role may be more nuanced when considering data distribution characteristics. Nevertheless, this finding aligns with previous research, suggesting that decreases in cognitive fusion may underlie increases in psychological flexibility and reduction in psychiatric symptoms across diagnoses documented in association with 5-MeO-DMT use to date (Davis, Averill, et al., 2020; Mangini et al., 2022).

Comparison with Other Psychedelics

These findings are consistent with research on other psychedelics, such as psilocybin, ayahuasca, and mescaline, which also demonstrate therapeutic potential through mechanisms like ego-dissolution and psychological insight. Studies on psilocybin, for instance, have shown that ego-dissolution can lead to significant reductions in symptoms of treatment-resistant depression (Roseman et al., 2018). Similarly, ayahuasca has been found to promote psychological insight, helping individuals gain new perspectives on their life challenges and fostering emotional well-being (Domínguez-Clavé et al., 2016). Additionally, research on mescaline has shown that acute experiences of psychological insight are associated with significant improvements across mental health conditions such as depression, anxiety, and substance use disorders (Agin-Liebes et al., 2021).

However, 5-MeO-DMT's rapid onset and intense effects set it apart from other psychedelics. The experience induced by 5-MeO-DMT typically begins within seconds to minutes after administration, peaking rapidly and often resulting in a profound and

overwhelming experience. This intense and fast-acting nature of 5-MeO-DMT may lead to more immediate and dramatic shifts in consciousness compared to psilocybin, ayahuasca or mescaline, which have slower onsets and longer durations of acute effects. Due to its unique properties, thorough integration practices are particularly important for 5-MeO-DMT. Integration involves the process of making sense of the psychedelic experience and helping individuals process their experiences, deriving meaningful insights, and applying these insights in ways that promote long-term psychological well-being and behavioral change (Bathje et al., 2022).

Moreover, the intensity of 5-MeO-DMT experiences can sometimes lead to challenging psychological states, including feelings of fear, confusion, or a sense of dreaded ego dissolution that might be difficult to integrate without proper support. This necessitates a well-designed framework for preparation to maximize the therapeutic benefits and mitigate potential adverse effects. Practices such as journaling (Tersavich, 2022), psychoeducation sessions (Yaden et al., 2022), peer support groups (Skiles et al., 2023), somatic-based practices and therapies such as somatic experiencing (Brom et al., 2017), and mindfulness exercises (Smigielski et al., 2019) can be beneficial components of preparation and integration processes tailored specifically for 5-MeO-DMT. These practices, in turn, may foster greater psychological insight, reduce the potential for challenging experiences, and facilitate improved well-being long-term.

Motivation for Using 5-MeO-DMT and the Role of Context of Use

Results of the present study suggest that respondents whose motivation to use 5-MeO-DMT was spiritual exploration had larger decreases in cognitive fusion (-1.99) compared to those using it for personal growth or experimentation reasons (-1.26). It could be the case that individuals motivated by spiritual exploration engage more deeply with the 5-MeO-DMT experience, potentially leading to more profound psychological shifts. Those using 5-MeO-DMT

for personal growth or experimentation might not engage as deeply, or their goals may be less focused on fundamental psychological shifts like decreases in cognitive fusion.

Moreover, spiritual exploration as a motivation likely involves a higher degree of intentionality and mental preparedness, which can enhance the therapeutic effects of 5-MeO-DMT. This intentionality may lead to a greater readiness to confront and integrate challenging aspects of the self, thus reducing cognitive fusion levels. Interestingly, although those using 5-MeO-DMT as a mental health treatment showed the largest decreases in cognitive fusion, these reductions did not reach statistical significance. Nevertheless, these results suggest that individuals with higher initial cognitive fusion – often those with mental health concerns – might experience the most significant decreases (Chen et al., 2023).

Future research should investigate how different motivations for using 5-MeO-DMT influence the depth and nature of the experience and its outcomes in upcoming prospective longitudinal studies. Qualitative studies can provide richer insights into how individuals with different motivations experience and integrate their 5-MeO-DMT experiences. Interviews and narrative analyses could uncover the subjective processes that contribute to the observed differences in cognitive fusion reductions.

The finding that respondents using 5-MeO-DMT in a church or ceremony context reported smaller decreases (-1.25) compared to those using it in their own or a friend's home/apartment (-1.96), suggests that the context of use plays a crucial role in the psychological outcomes of 5-MeO-DMT experiences. The structured and ritualistic nature of ceremonial settings may emphasize collective spiritual experiences over individual psychological work, while personal settings may facilitate deeper introspection and emotional processing. These results highlight the need for further research into how different environments influence the

therapeutic potential of 5-MeO-DMT, including qualitative studies on subjective experiences and mechanistic studies on contextual factors.

Challenging Experiences and Psychological Insight Predict Cognitive Fusion Decreases

Our hypothesis that greater intensity of challenging and psychological effects would be associated with greater decreases in cognitive fusion was supported by the present findings. This is consistent with prior studies showing that challenging psychedelic experiences can lead to long-term improvements in well-being and life satisfaction (Carbonaro et al., 2016). With this in mind, it is possible that challenging experiences that result from using 5-MeO-DMT, by enabling individuals to make contact with difficult emotions and cognitions, which under normal waking consciousness are otherwise avoided, can lead to emotional breakthrough experiences of insight (Roseman et al., 2019). The emotional breakthrough experience is a recently conceived construct that encompasses precisely the process of facing challenging emotions and memories during the acute effects of a psychedelic experience, and being able to transcend these difficulties, thereby coming to a sense of completion or resolution (Johansen et al., 2022). In line with the idea that 5-MeO-DMT-induced challenging experiences could facilitate emotional breakthrough resulting in psychological flexibility via decreases in cognitive fusion, emotional breakthrough experiences during the acute psychedelic effects have indeed been associated with greater improvements in psychological flexibility (Close et al., 2020). Future studies should continue to explore these associations to enhance the therapeutic potential of 5-MeO-DMT for specific targeted indications.

Furthermore, our finding that greater ratings of psychological insight were associated with larger decreases in cognitive fusion is also concordant with prior studies that have shown psychological insight was a robust predictor of psychedelics' therapeutic effects across various

psychiatric symptoms, including depression, anxiety and substance misuse (Agin-Liebes et al., 2021; Davis, Barrett, et al., 2020; Davis, Barrett, May, et al., 2021; Davis, Xin, et al., 2021; Garcia-Romeu et al., 2020; Garcia-Romeu et al., 2019). Moreover, prior studies have demonstrated that increases in psychological flexibility predicted significant reductions in PTSD symptoms following 5-MeO-DMT treatment (Davis, Averill, et al., 2020; Mangini et al., 2022). These findings align with the present study's observation of significant decreases in cognitive fusion from before-to-after 5-MeO-DMT use, offering preliminary convergent support to the hypothesis that increases in psychological flexibility associated to 5-MeO-DMT use in therapeutic contexts could be driven by decreases in cognitive fusion.

Longer Time Planned Ahead Predicts Cognitive Fusion Decreases

The present study findings showed that respondents who planned ahead longer for their 5-MeO-DMT experience reported larger decreases in cognitive fusion levels. This suggests that those who proactively approach a 5-MeO-DMT experience may derive greater therapeutic benefit than those who approach it more casually. By planning ahead, individuals may create a mental framework that enhances their readiness to engage deeply with the 5-MeO-DMT experience, potentially facilitating more significant psychological shifts and long-term positive outcomes. This finding aligns with other research (Chapter 3 of this dissertation) suggesting that planning ahead and setting intentions may support processes related to self-directed behavior change and neuroplasticity.

This association between longer planning time and larger decreases in cognitive fusion, even when controlling for acute effects, may reflect an intentional process of self-directed behavior change a person who approaches a 5-MeO-DMT proactively may be engaged in. Self-directed behavior refers to the capacity to self-regulate one's thoughts, feelings, and impulses in

ways that allow one to modify behaviors to gain desirable outcomes (Watson & Tharp, 1989). This concept is consistent with the ACT's model emphasis on value-based behaviors (Harris, 2019), where the goal is to increase the ability to persist or change behavior in the service of one's chosen values, ultimately improving quality of life and well-being (Hayes et al., 2013).

Interestingly, longer time planned ahead for a 5-MeO-DMT experience was previously shown to be associated with greater likelihood of reactivations (Ortiz Bernal et al., 2022). Reactivations refer to subjective experiences that may occur days, weeks or months after a 5-MeO-DMT dose, in which a person may feel like they are re-experiencing some aspect of the acute effects they experienced during their 5-MeO-DMT dosing session. Findings to date suggest that reactivations are mostly experienced as positive or neutral experiences (Ortiz Bernal et al., 2022). Ortiz Bernal (this dissertation; Chapter 3) also showed that longer time planned ahead for a 5-MeO-DMT dose, as well as decreases in cognitive fusion from before-to-after 5-MeO-DMT use were associated with greater likelihood of reactivation events.

These findings highlight the importance of preparation and intention setting in maximizing the therapeutic potential of 5-MeO-DMT use. In line with this, results from a study by Lancelotta and Davis (2020) offer convergent support for the idea that proactively preparing for a 5-MeO-DMT dose (by planning ahead), and having a specific intention for the dosing session can serve as a catalyst for values-based, self-directed behavioral changes leading to greater well-being. In their study, Lancelotta and Davis examined the effects of the utilization of a series of harm reduction strategies, which they have renamed "benefic enhancement strategies." One of the benefit enhancement strategies most commonly endorsed is precisely to focus on a specific intention for the 5-MeO-DMT dosing session. Setting an intention has in turn been associated with more intense mystical-type effects, less intense challenging experiences,

and greater meaningfulness attributed to the experience long-term (Lancelotta & Davis, 2020). In general terms, the present study's finding of longer time planned ahead being associated with larger decreases in cognitive fusion seems in line with the general notion that 5-MeO-DMT, being the powerful psychedelic substance it is, warrants extensive preparation and readiness on the part of users in order to maximize the potential for positive effects long-term, and minimize any adverse effects. Future longitudinal studies could track how preparation and intention-setting impact both immediate and long-term therapeutic outcomes.

Increases in Nature Relatedness and Prosocial Behavioral Intentions

Our hypothesis that greater intensity of acute effects would be associated with greater increases in nature relatedness was not supported by the present results, suggesting that these changes may result from a more gradual integration process, influenced by changes in life perspective, or shifts in personal values that unfold over time, rather than immediate psychedelic experiences. Furthermore, it's possible that the constructs of ego-dissolution, psychological insight, and challenging experiences, while impactful, are not directly responsible for changes in nature relatedness. There might be other psychological factors at play that were not measured in the study, such as feelings of interconnectedness (Kałużna et al., 2022; Watts et al., 2022), or shifts in environmental awareness that are more directly related to nature relatedness.

Future research should explore the mechanisms underlying increases in nature relatedness following 5-MeO-DMT use. Given that acute effects do not appear to be directly responsible, longitudinal studies are needed to examine how nature relatedness evolves over time and what specific factors contribute to these changes. These studies could investigate the role of gradual shifts in life perspective and personal values, as well as the impact of long-term integration

practices, and other potentially more relevant constructs such as interconnectedness (Watts et al., 2022).

Increases in prosocial behavioral intentions were only associated with greater ratings of acute challenging experiences related to 5-MeO-DMT use. Challenging experiences during the acute psychedelic state have been correlated with the occurrence of mystical-type experiences (Bradstreet et al., 2014), which in turn have been found to predict long-term therapeutic effects, as well as increases in the personality domain of openness (MacLean et al., 2011). Follow up qualitative studies with participants from psilocybin trials, including a trial for treatment-resistant depression (Watts et al., 2017), depression associated with a terminal diagnosis (Belser et al., 2017), and smoking cessation (Noorani et al., 2018), have consistently reported themes of connection, acceptance, and insight. Watts et al. (2017) identified two main processes of change facilitated by psilocybin: 1) a change from disconnection to connection (to self, others, world); and 2) a change from avoidance to acceptance (of negative emotions). Belser et al (2017) also documented that periods of intense emotional states (challenging experiences) served as the "turning point" for waves of emotional catharsis and self-compassion, ultimately leading to sustained well-being (Belser et al., 2017).

The profound ego-dissolution induced by 5-MeO-DMT may initially produce a challenging experience due to its intensity and rapid onset overwhelmingly compelling users to let go and accept rather than resist the experience. This process of surrendering, even when facing acute difficulties like feelings of "dying" or post-dose challenges such as night terrors (Ragnhildstveit et al., 2023), may nevertheless lead to new psychological insights, and alleviation of clinical symptoms (Wolff et al., 2020). By facing these challenging experiences rather than avoiding, individuals may break through difficult mental and emotional states

(Kangaslampi, 2023). This can potentially result in enhanced self-compassion and a sense of "shared humanity," as described by Watts et al. (2017).

In the current study, this phenomenon of shared humanity was suggested by the association between higher ratings of challenging experiences and increased prosocial behavioral intentions. Future research could empirically test this theoretical framework to further understand how challenging experiences in 5-MeO-DMT sessions may foster greater levels of prosocial behavior and well-being long-term.

Predictors of Persisting Positive Changes

Besides decreases in cognitive fusion, significant predictors of persisting positive changes attributed to the 5-MeO-DMT experience in the OLS regression models were older age at time of 5-MeO-DMT use, and greater ego-dissolution effects. Older age being associated with positive persisting effects is consistent with prior 5-MeO-DMT findings (Ortiz Bernal et al., 2022). Furthermore, prior psychedelic studies have found that profound feelings of awe and an enhanced capacity for perceiving beauty appear to be the result of the ego-dissolution and peak experiences people report (Belser et al., 2017; Noorani et al., 2018; Watts et al., 2017). Previous studies have also related the ego-dissolution effects elicited by 5-MeO-DMT use to an overwhelming sense of “oneness” people feel that can elicit an emotional change in perspective that leads to improved mood and quality of life (Davis et al., 2018; Reckweg et al., 2022; Uthaug et al., 2019). Our present finding of ego-dissolution effects predicting long-term enduring positive changes related to life satisfaction and well-being are in alignment with prior findings (Uthaug et al., 2019; Uthaug et al., 2018), and suggest the ego-dissolution experiences may be central to the positive therapeutic effects documented in association to 5-MeO-DMT use to date.

Neither increases in nature relatedness, nor in prosocial behavioral intentions were associated with greater ratings of persisting positive changes. Our hypotheses that greater ratings of persisting effects would be associated with decreases in cognitive fusion, and increases in nature relatedness and prosocial behavioral intentions was only supported for cognitive fusion decreases in the OLS model. However, once the non-normality of the data was addressed with the Tobit model, decreases in cognitive fusion did not have a statistically significant impact on persisting effects.

The Tobit regression models provided additional insights by addressing the skewness and non-normality of the data. In these models, older age and greater ego-dissolution remained significant predictors of persisting positive change, consistent with the OLS findings. Notably, the Tobit models revealed that motivation for using 5-MeO-DMT also emerged as a significant predictor of positive persisting changes. Specifically, respondents who used 5-MeO-DMT as a mental health treatment reported significantly higher persisting positive effects compared to those who used it for spiritual exploration. This finding highlights the importance of understanding individual motivations for using 5-MeO-DMT, as those seeking mental health treatment may experience more substantial long-term benefits.

This ties into the earlier observation that individuals using 5-MeO-DMT as a mental health treatment showed the largest, albeit not statistically significant, decreases in cognitive fusion. It suggests that those with higher initial cognitive fusion (i.e., clinical populations), might benefit most from 5-MeO-DMT, particularly when their use is motivated by a desire for mental health improvement in a specific condition. The significant positive effects observed in the Tobit model underscore the potential for 5-MeO-DMT to facilitate meaningful psychological change, especially for those with targeted therapeutic goals. Future clinical trials should investigate the

potential of 5-MeO-DMT as a specifically tailored treatment for conditions such as PTSD (Ragnhildstveit et al., 2023), and others such as prolonged grief disorder (Ehrenkranz et al., 2024; Low & Earleywine, 2023).

Implications for Spanish-speaking Populations

The findings of this study have significant implications for the inclusion of Spanish-speaking populations in psychedelic research. By demonstrating that 5-MeO-DMT can induce meaningful psychological changes in this demographic, the study highlights and reiterates the importance of cultural context in psychedelic experiences. The results suggest that incorporating diverse linguistic and cultural perspectives can enrich our understanding of 5-MeO-DMT's therapeutic potential. Future research should continue to prioritize the inclusion of underrepresented groups to ensure that psychedelic therapies are effective and relevant across different cultural settings.

Clinical Implications and Future Research Directions

These findings have several clinical implications. For example, they suggest that 5-MeO-DMT could be particularly beneficial for individuals with high cognitive fusion, such as those with mental health concerns. The results also underscore the importance of proactively preparing for the 5-MeO-DMT experience to maximize therapeutic benefits.

Much more research is needed to systematically examine these processes in rigorous trials employing prospective, mixed methods, longitudinal designs. Future studies investigating 5-MeO-DMT's therapeutic potential may help expand this work by assessing cognitive fusion in studies aimed at evaluating its efficacy for a specific psychiatric diagnosis. If other studies were to see a similar trend of findings, it may be worthwhile to include psychoeducation modules related to cognitive defusion strategies as part of the preparation sessions prior to dosing to

further enhance long-term treatment outcomes. Similarly, integration sessions following 5-MeO-DMT administration could be structured around making a plan for the participant to continue practicing defusion strategies to sustain treatment gains.

Strengths and Study Limitations

A key strength of the present study is its focus on a Spanish-speaking sample, addressing the limitations of previous studies predominantly conducted with young White males (Agin-Liebes et al., 2021; Davis, Barrett, et al., 2020; Davis et al., 2018), which may limit the generalizability of findings to other demographic groups (George et al., 2020; Michaels et al., 2018). This contributes to the diversification of respondents in psychedelic research, a critical need highlighted by researchers in the field (Williams et al., 2023; Williams & Labate, 2019; Williams et al., 2020). To our knowledge, this is the first investigation to explore decreases in cognitive fusion within the context of 5-MeO-DMT therapy and research. The significant findings of the present study offer preliminary support for the relevance of this construct in understanding the transdiagnostic therapeutic applications of 5-MeO-DMT.

Several limitations of this study warrant consideration and caution when interpreting the results. First, the cross-sectional design of the survey precludes any inference of causality between 5-MeO-DMT use and changes in the psychological constructs examined herein. Second, retrospective survey studies are limited by recall bias (Coughlin, 1990), which may increase the likelihood that current affect influences recollection of subjective psychedelic experiences. Third, results are also limited by possible self-selection by individuals favorably inclined toward 5-MeO-DMT experiences. Considering that recruitment took place primarily via social media, email, and word-of-mouth, it is possible that respondents were biased in their predisposition and willingness to be publicly affiliated with others who have used 5-MeO-DMT.

Notwithstanding these limitations, the study findings are important because they provide preliminary evidence of the mechanisms that may underlie the potential therapeutic effects of 5-MeO-DMT. They also highlight the need for further research to explore these effects in more controlled settings and diverse populations. This study contributes to the growing body of literature on 5-MeO-DMT research and therapy, and underscores the significance of understanding the psychological mechanisms involved in 5-MeO-DMT experiences.

Conclusion

In conclusion, our study found significant decreases in cognitive fusion, and increases in nature relatedness and prosocial behavioral intentions from before-to-after 5-MeO-DMT use. Challenging experiences and psychological insight were key predictors of these changes. Ego-dissolution effects, while not directly associated with cognitive fusion, nature relatedness, or prosocial behavioral intentions, were strongly associated with persisting positive changes related to life satisfaction and well-being, including improved attitudes, relationships, and behavioral patterns that respondents attributed to their 5-MeO-DMT experience.

Our study findings suggest that there may be two potentially independent paths to enhanced 5-MeO-DMT positive persisting effects: one through acute ego-dissolution experiences, and the other through cognitive fusion decreases post-dose. The finding that longer time planned ahead for a 5-MeO-DMT dose was associated with larger decreases in cognitive fusion suggests that individuals who proactively approach a 5-MeO-DMT may be mindfully engaged in a process of self-directed change that is supported by these cognitive fusion decreases. These decreases appear to translate into greater positive persisting changes related to overall life satisfaction and well-being that individuals attribute to their 5-MeO-DMT experience.

Much remains to be explored and examined in the burgeoning field of psychedelic science. The prospect of integrating 5-MeO-DMT research within a psychological flexibility model appears to hold promise in enhancing its beneficial effects on mental health. This integration may support processes of positive change and holistic well-being by reducing cognitive fusion and promoting greater psychological flexibility.

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Tables

Table 1

Demographic Data and 5-MeO-DMT Use Patterns (*n*=90)

Characteristic	*M (SD) or %*
Age	38.89 (11.57)
Sex	
Male	67%
Female	33%
Education	
Graduated high school/trade or technical school	17%
Some college – no degree	29%
Associate degree/bachelor's degree	35%
Advanced degree (Master's, Ph.D., M.D.)	19%
Country of Origin	
México	53%
South American countries	28%
Central American countries	3%
European countries	6%
United States	9%
Age at time of experience	35.02 (11.93)
Motivation for using	
Spiritual exploration	43%
Mental health treatment	21%
Personal growth & experimentation	36%
Location of use	
Own/Friend's apartment/house	27%
Outdoors – nature setting	50%
Church/Ceremony/Treatment center/Other	23%
Planned Time Ahead	
No plan or a few days	49%
One week/one month/>six months)	51%

Table 2

Comparison of Retrospective Ratings of Cognitive Fusion, Nature Relatedness and Prosocial Behavioral Intentions from Before and After 5-MeO-DMT Use (*n*=90).

Variable	Before 5-MeO-DMT *M (SD)*	After 5-MeO-DMT *M (SD)*	Change Score[a] *M (SD)*	*t*-test[b]	Effect size Cohen´s *d*
Cognitive fusion	4.41 (1.60)	2.70 (1.15)	-1.71 (1.36)	-11.90***	-1.25
Nature relatedness	3.54 (1.03)	4.57 (0.71)	1.03 (1.10)	8.85***	0.93
Prosocial behavioral intentions	5.4 (1.12)	6.19 (0.86)	.79 (0.98)	7.67***	0.80

***p <.001

[a]Score range for each measure: Cognitive fusion (1-7); Nature relatedness (1-5); Prosocial behavioral intentions (1-7). Decreases in CF represent an improvement. Higher scores in NR and PSB indicate improvement.

[b]*t*-test: Because the distribution of these scores was non-normal, Wilcoxon signed-rank tests were used to compare before and after scores. All tests remained statistically significant, p<.001, and effect sizes tests remained large: Cognitive fusion r = -0.85; nature relatedness r = 0.80; prosocial behavioral intentions r = 0.71.

Table 3

Hierarchical Regression Analyses to Examine Predictors of Changes in Cognitive Fusion (*n*=90)

	Model 1	Model 2	Model 3
Block 1: Demographic	*B (SE)*	*B (SE)*	*B (SE)*
Intercept	-1.71*** (.14)	-1.99*** (.31)	-1.96*** (.27)
Age at time of 5-MeO-DMT use	-0.01 (.01)	-0.01 (.01)	-0.01 (.01)
Likelihood-ratio test M1 - M2 = χ^2 = 19.67, *p* =.001			
Block 2: Use characteristics			
Motivation for using			
-*Spiritual exploration (ref)*			
-Mental health treatment		-0.23 (.36)	-0.21 (.32)
-Personal growth/Experimentation		0.73* (.30)	0.36 (.28)
Location of use			
-*Own or friend's apartment/house (ref)*			
-Outdoors – nature setting		0.56 (.33)	0.59* (.29)
-Church/Ceremony/Treatment center		0.90* (.40)	0.71* (.36)
Time planned ahead			
-*No plan or a few days (ref)*			
-One week or more		-0.81** (.27)	-0.57* (.25)
Incremental R^2		19%	
Likelihood-ratio test M2 - M3 = χ^2 = 25.32, *p* <.001			
Block 3: Acute effects			
Ego Dissolution			-0.15 (.12)
Challenging Experiences			-0.28* (.13)
Psychological Insight			-0.39*** (.11)
Incremental R^2			20%
Total R^2	1%	20%	40%

Note. *p< .05; **p<.01; ***p<.001
M = model
Ref = reference category

Table 4

Hierarchical Regression Analyses to Examine Predictors of Changes in Nature Relatedness (*n*=90)

	Model 1	Model 2	Model 3
Block 1: Demographic	*B (SE)*	*B (SE)*	*B (SE)*
Intercept	1.03*** (.12)	1.10*** (.27)	-1.08*** (.27)
Age at time of 5-MeO-DMT use	-0.00 (.00)	-0.00 (.01)	-0.00 (.01)
Likelihood-ratio test M1 - M2 = $\chi^2 = 6.70$, $p = .243$			
Block 2: Use characteristics			
Motivation for using			
-*Spiritual exploration (ref)*			
-Mental health treatment		-0.17 (.32)	-0.16 (.32)
-Personal growth/Experimentation		-0.55* (.27)	-0.44 (.28)
Location of use			
-*Own or friend's apartment/house (ref)*			
-Outdoors – nature setting		0.20 (.29)	0.19 (.29)
-Church/Ceremony/Treatment center		-0.23 (.35)	-0.12 (.35)
Time planned ahead			
-*No plan or a few days (ref)*			
-One week or more		0.23 (.24)	0.14 (.25)
Incremental R^2		7%	
Likelihood-ratio test M2 - M3 = $\chi^2 = 2.94$, $p = .401$			
Block 3: Acute effects			
Ego Dissolution			0.16 (.12)
Challenging Experiences			0.08 (.12)
Psychological Insight			0.03 (.11)
Incremental R^2			3%
Total R^2	0%	7%	10%

Note. *p<.05; **p<.01; ***p<.001
M= model
Ref = reference category

Table 5

Hierarchical Regression Analyses to Examine Predictors of Changes in Prosocial Behavioral Intentions (*n*=90)

	Model 1	Model 2	Model 3
Block 1: Demographic	*B (SE)*	*B (SE)*	*B (SE)*
Intercept	0.79*** (.10)	0.70** (.23)	0.67** (.23)
Age at time of 5-MeO-DMT use	0.00 (.00)	-0.00 (00)	-0.00 (.00)
Likelihood-ratio test M1 - M2 = $\chi^2 = 11.62$, $p = .040$			
Block 2: Use characteristics			
Motivation for using			
-*Spiritual exploration (ref)*			
-Mental health treatment		-0.39 (.27)	-0.39 (.27)
-Personal growth/Experimentation		-0.47* (.23)	-0.32 (.23)
Location of use			
-*Own or friend's apartment/house (ref)*			
-Outdoors – nature setting		0.12 (.25)	0.08 (.24)
-Church/Ceremony/Treatment center		0.15 (.30)	0.25 (.30)
Time planned ahead			
-*No plan or a few days (ref)*			
-One week or more		0.49* (.20)	0.42* (.21)
Incremental R^2		12%	
Likelihood-ratio test M2 - M3 = $\chi^2 = 8.70$, $p = .033$			
Block 3: Acute effects			
Ego Dissolution			0.13 (.10)
Challenging Experiences			0.24* (.10)
Psychological Insight			0.04 (.09)
Incremental R^2			8%
Total R^2	0%	12%	20%

Note. *p<.05; **p<.01; ***p<.001
M= model
Ref = reference category

Table 6a

Hierarchical Regression Analyses to Examine the Associations Between Persisting Effects of 5-MeO-DMT use and Changes in Cognitive Fusion *(n*=90*)*

	Model 1	Model 2	Model 3	Model 4
Block 1: Demographic	B (SE)	B (SE)	B (SE)	B (SE)
Intercept	24.77*** (1.34)	23.06*** (3.15)	22.52*** (2.90)	27.24*** (3.64)
Age at time of 5-MeO-DMT use	0.30* (.11)	0.29* (.12)	0.28* (.11)	0.31* (.11)
Likelihood-ratio test M1 - M2= $\chi^2 = 3.60$, $p = .609$				
Block 2: Use characteristics				
Motivation for using				
-*Spiritual exploration (ref)*				
-Mental health treatment		4.64 (3.71)	5.11 (3.42)	5.62 (3.36)
-Personal growth/Experimentation		-0.68 (3.14)	1.72 (3.00)	0 .85 (2.97)
Location of use				
-*Own or friend's apartment/house (ref)*				
-Outdoors – nature setting		-0.39 (3.38)	-0.54 (3.12)	-1.95 (3.13)
-Church/Ceremony/Treatment center		-0.59 (4.04)	2.56 (3.80)	0.84 (3.81)
Time planned ahead				
-*No plan or a few days (ref)*				
-One week or more		2.53 (2.78)	0.44 (2.65)	1.82 (2.68)
Incremental R^2		4%		
Likelihood-ratio test M2 - M3 = $\chi^2 = 18.25$, $p < .001$				
Block 3: Acute effects				
Ego Dissolution			5.46*** (1.31)	5.82*** (1.30)
Challenging Experiences			1.46 (1.33)	2.13 (1.34)
Psychological Insight			-0.82 (1.17)	0.11 (1.23)
Incremental R^2			16%	

Likelihood-ratio test M3 - M4 = χ^2 = 4.77, *p* =.029				
Block 4: Psychological changes				
Cognitive fusion				2.41* (1.16)
Incremental R^2				4%
Total R^2	8%	12%	28%	32%

Note. *p<.05; **p<.01; ***p<.001
M= model
Ref = reference category

Table 6b

Tobit Regression Analysis to Examine the Associations Between Persisting Effects of 5-MeO-DMT use and Changes in Cognitive Fusion (*n*=90)

Variable	*B (SE)*	*P* value	95% Confidence Interval
Intercept	28.15 (4.21)	<.001*	19.75 – 36.55
Age at time of experience	0.44 (0.13)	.001*	.19 – .70
Motivation for using			
- *Spiritual exploration (ref)*			
- Mental health treatment	9.45 (4.11)	.024*	1.26 – 17.63
- Personal growth/Experimentation	1.35 (3.40)	.691	-5.40 – 8.10
Location of use			
- *Own or friend's apartment (ref)*			
- Outdoors	-0.44 (3.60)	.904	-7.60 – 6.73
- Church/Ceremony/Treatment Center	1.51 (4.37)	.730	-7.18 – 10.21
Time planned ahead	0.10 (3.11)	.976	-6.10 – 6.29
Acute effects			
Ego-dissolution	6.95 (1.48)	<.001*	4.00 – 9.90
Challenging experiences	2.51 (1.57)	.114	-.61 – 5.64
Psychological insight	0.88 (1.43)	.541	-1.98 – 3.73
Psychological changes			
Decreases in cognitive fusion	2.06 (1.37)	.136	-.66 – 4.78

*Note: ref = reference category, *p = <.05*
Log likelihood = -287.99
Prob >*Chi2* = <.001
Pseudo R^2 = 0.062

Table 7a

Hierarchical Regression Analyses to Examine the Associations Between Persisting Effects of 5-MeO-DMT use and Changes in Nature Relatedness (*n*=90)

	Model 1	Model 2	Model 3	Model 4
Block 1: Demographic	B (SE)	B (SE)	B (SE)	B (SE)
Intercept	24.77*** (1.34)	23.06*** (3.15)	22.52*** (2.90)	22.48*** (3.64)
Age at time of 5-MeO-DMT use	0 .30* (.11)	0 .29* (.12)	0.28* (.11)	0.28* (.11)
Likelihood-ratio test M1 - M2 = $\chi^2 = 3.60$, $p = .609$				
Block 2: Use characteristics				
Motivation for using				
-*Spiritual exploration (ref)*				
-Mental health treatment		4.64 (3.71)	5.11 (3.42)	5.11 (3.45)
-Personal growth/Experimentation		-0.68 (3.14)	1.72 (3.00)	1.74 (3.06)
Location of use				
-*Own or friend's apartment/house (ref)*				
-Outdoors – nature setting		-0.39 (3.38)	-0.54 (3.12)	-0.55 (3.15)
-Church/Ceremony/Treatment center		-0.59 (4.04)	2.56 (3.80)	2.56 (3.82)
Time planned ahead				
-*No plan or a few days (ref)*				
-One week or more		2.53 (2.78)	0.44 (2.65)	0.43 (2.67)
Incremental R^2		4%		
Likelihood-ratio test M2 - M3 = $\chi^2 = 18.25$, $p < .001$				
Block 3: Acute effects				
Ego Dissolution			5.46*** (1.31)	5.45*** (1.33)
Challenging Experiences			1.46 (1.33)	1.46 (1.34)
Psychological Insight			-0.82 (1.17)	-0.82 (1.19)
Incremental R^2			16%	
Likelihood-ratio test M3 - M4 = $\chi^2 = 0.00$, $p = .968$				

Block 4: Psychological changes				
Nature relatedness				0.05 (1.20)
Incremental R^2				0%
Total R^2	8%	12%	28%	28%

Note. *p<.05; **p<.01; ***p<.001
M= model
Ref = reference category

Table 7b

Tobit Regression Analysis to Examine the Associations Between Persisting Effects of 5-MeO-DMT use and Changes in Nature Relatedness (*n*=90)

Variable	*B (SE)*	*P* value	95% Confidence Interval
Intercept	23.13 (3.70)	<.001*	15.75 – 30.50
Age at time of experience	0.42 (0.13)	.002*	.16 – .68
Motivation for using			
- *Spiritual exploration (ref)*			
- Mental health treatment	9.30 (4.22)	.030*	.90 – 17.70
- Personal growth/Experimentation	2.63 (3.48)	.452	-4.30 – 9.55
Location of use			
-*Own or friend's apartment (ref)*			
- Outdoors	.64 (3.60)	.860	-6.54 – 7.81
- Church/Ceremony/Treatment Center	3.38 (4.34)	.440	-5.27 – 12.02
Time planned ahead	-1.19 (3.08)	.701	-7.32 – 4.95
Acute effects			
Ego-dissolution	6.57 (1.52)	<.001*	3.54 – 9.60
Challenging experiences	1.87 (1.56)	.233	-1.23 – 4.98
Psychological insight	0.10 (1.38)	.939	-2.64 – 2.85
Psychological changes			
Increases in nature relatedness	0.89 (1.44)	.537	-1.97 – 3.75

*Note: ref = reference category, *p = <.05*
Log likelihood = -288.90
Prob >*Chi2* = <.001
Pseudo R^2 = 0.060

Table 8a

Hierarchical Regression Analyses to Examine the Associations Between Persisting Effects of 5-MeO-DMT use and Prosocial Behavioral Intentions (n=90)

	Model 1	Model 2	Model 3	Model 4
Block 1: Demographic	B (SE)	B (SE)	B (SE)	B (SE)
Intercept	24.77*** (1.34)	23.06*** (3.15)	22.52*** (2.90)	21.76*** (3.07)
Age at time of 5-MeO-DMT use	0.30* (.11)	0.29* (.12)	0.28* (.11)	0.28* (.11)
Likelihood-ratio test M1 - M2 = $\chi^2 = 3.60$, $p = .609$				
Block 2: Use characteristics				
Motivation for using				
-*Spiritual exploration (ref)*				
-Mental health treatment		4.64 (3.71)	5.11 (3.42)	5.54 (3.48)
-Personal growth/Experimentation		-0.68 (3.14)	1.72 (3.00)	2.08 (3.04)
Location of use				
-*Own or friend's apartment/house (ref)*				
-Outdoors – nature setting		-0.39 (3.38)	-.54 (3.12)	-0.62 (3.13)
-Church/Ceremony/Treatment center		-0.59 (4.04)	2.56 (3.80)	2.27 (3.82)
Time planned ahead				
-*No plan or a few days (ref)*				
-One week or more		2.53 (2.78)	0.44 (2.65)	-0.03 (2.73)
Incremental R^2		4%		
Likelihood-ratio test M2 - M3 = $\chi^2 = 18.25$, $p < .001$				
Block 3: Acute effects				
Ego Dissolution			5.46*** (1.31)	5.31*** (1.33)
Challenging Experiences			1.46 (1.33)	1.18 (1.38)
Psychological Insight			-0.82 (1.17)	-0 .87 (1.18)
Incremental R^2			16%	
Likelihood-ratio test M3 - M4 = $\chi^2 = 0.70$, $p = .403$				

Block 4: Psychological changes				
Prosocial behavioral intentions				1.13 (1.44)
Incremental R^2				1%
Total R^2	8%	12%	28%	29%

Note. *p<.05; **p<.01; ***p<.001
M= model
Ref = reference category

Table 8b

Tobit Regression Analysis to Examine the Associations Between Persisting Effects of 5-MeO-DMT use and Changes in Prosocial Behavioral Intentions (*n*=90)

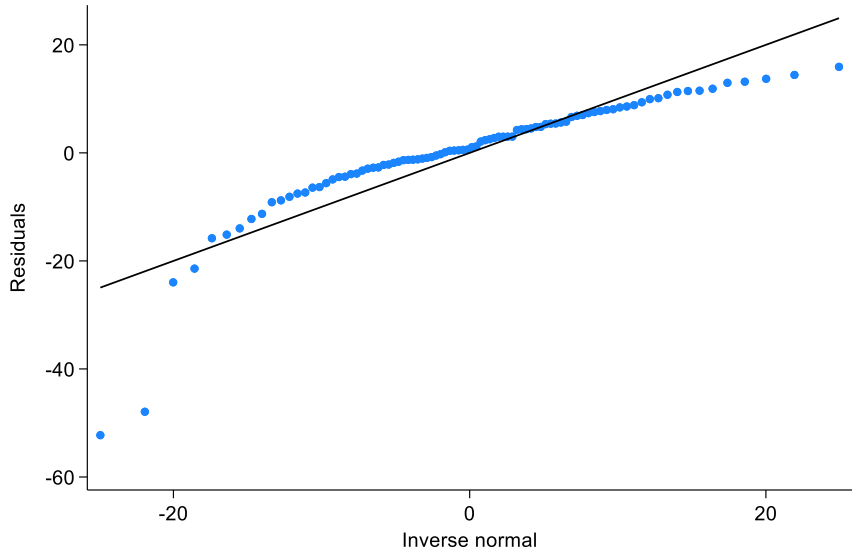
Variable	*B (SE)*	*P* value	95% Confidence Interval
Intercept	23.05 (3.50)	<.001*	16.06 – 30.03
Age at time of experience	0.43 (0.13)	.001*	.17 – .68
Motivation for using			
Spiritual exploration (ref)			
Mental health treatment	9.64 (4.21)	.025*	1.25 – 18.03
Personal growth/Experimentation	2.79 (3.46)	.422	-4.09 – 9.67
Location of use			
Own or friend's apartment (ref)			
Outdoors	.54 (3.60)	.880	-6.60 – 7.69
Church/Ceremony/Treatment Center	2.82 (4.34)	.517	-5.80 – 11.45
Time planned ahead	-1.72 (3.13)	.583	-7.95 – 4.50
Acute effects			
Ego-dissolution	6.50 (1.51)	<.001*	3.50 – 9.52
Challenging experiences	1.52 (1.60)	.347	-1.67 – 4.71
Psychological insight	0.52 (1.37)	.970	-2.67 – 2.78
Psychological changes			
Increases in prosocial behavioral intentions	1.62 (1.74)	.355	-1.84 – 5.07

*Note: ref = reference category, *p = <.05*
Log likelihood = -288.66
Prob >*Chi2* = <.001
Pseudo R^2 = 0.060

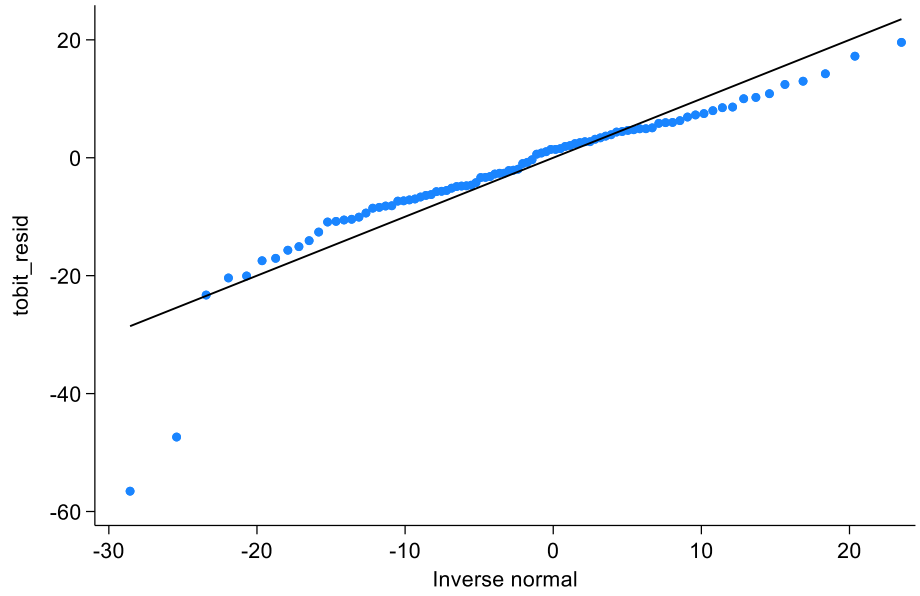
Appendix 1

Residual Plots of OLS and Tobit Models Examining Persisting Effects and Changes in Cognitive Fusion (Model 4)

OLS Model Q-Q Plot



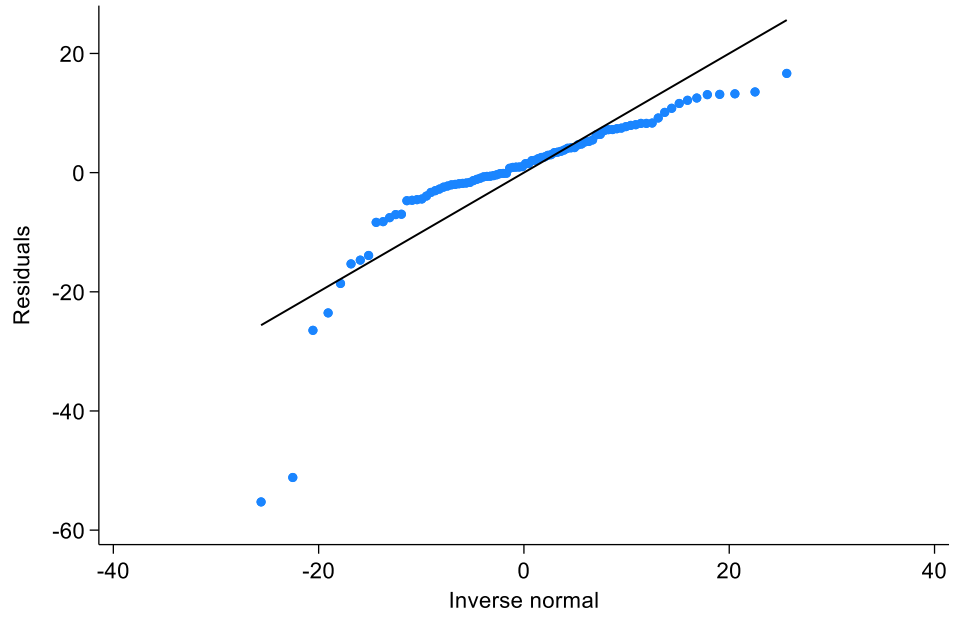
Tobit Model Q-Q Plot



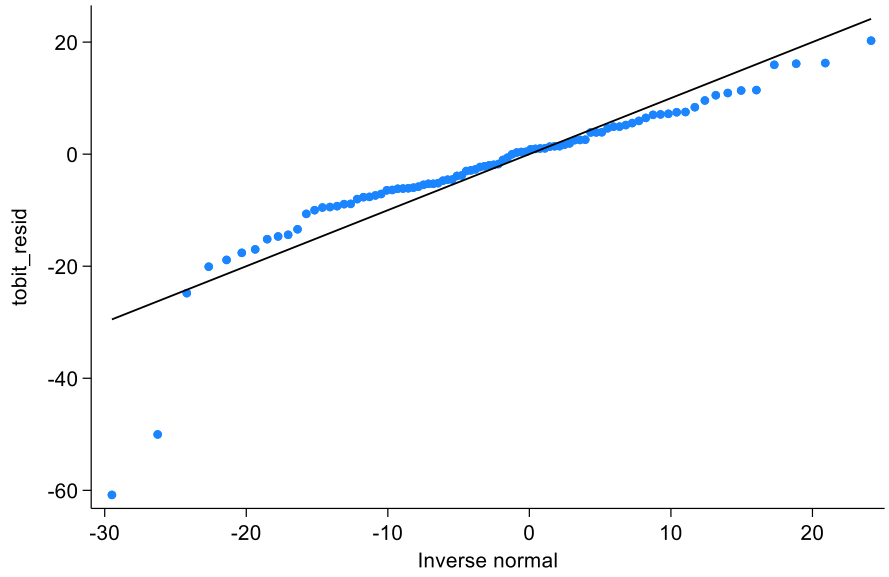
Appendix 2

Residual Plots of OLS and Tobit Models Examining Persisting Effects and Changes in Nature Relatedness (Model 4)

OLS Model Q-Q Plot



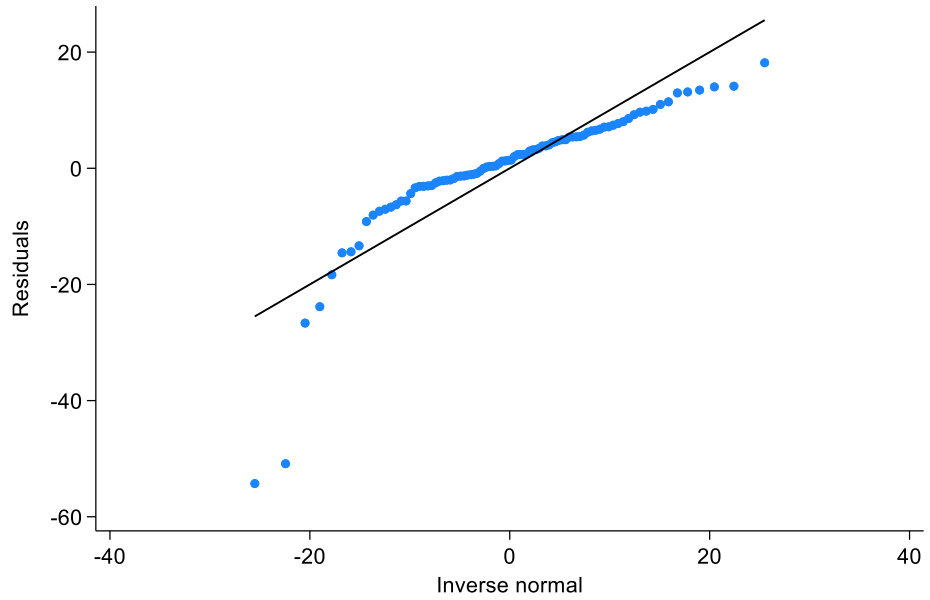
Tobit Model Q-Q Plot



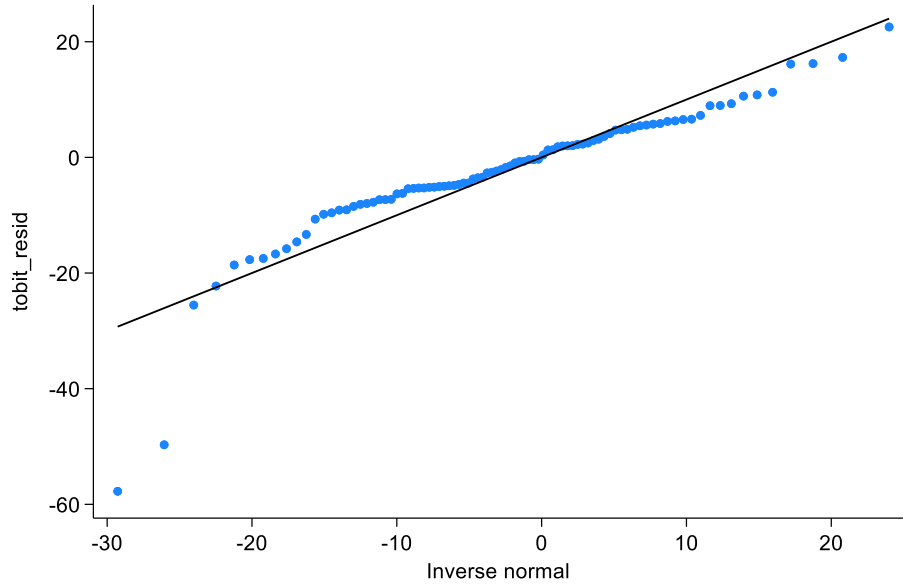
Appendix 3

Residual Plots of OLS and Tobit Models Examining Persisting Effects and Changes in Prosocial Behavioral Intentions (Model 4)

OLS Model Q-Q Plot



Tobit Model Q-Q Plot



Chapter 3 - Reactivations Associated with the Use of 5-MeO-DMT among Spanish-speaking Individuals: Prevalence, Predictors, and Emotional Valence

Abstract

Background: 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a psychedelic gaining interest as a potential mental health treatment. However, a poorly characterized phenomenon termed reactivation (similar to "flashbacks") appears to be commonly associated with its use and merits investigation.

Aims: We examined the prevalence, predictors, and emotional valence of reactivations among a sample of Spanish-speaking individuals. Specifically, we investigated whether gender, time planned ahead, intensity of acute effects, and the meaningfulness attributed to the experience predicted reactivation events. Additionally, we explored whether decreases in cognitive fusion were associated with reactivations and whether these predictors influenced the positive versus neutral/negative emotional valence of these experiences.

Materials and Method: A cross-sectional survey study was conducted with 90 participants. Descriptive statistics and logistic regression analyses were employed to examine the aims.

Results: Sixty-nine percent of respondents reported reactivations, with 97% indicating it was a positive or neutral experience. In the multivariable logistic regression model, longer time planned ahead and decreases in cognitive fusion were significant predictors of reactivations. Challenging experiences were associated with a lower likelihood of reactivations being perceived as positive, while psychological insight was associated with a higher likelihood of positive perceptions.

Conclusion: Reactivations among this sample appear to be a common phenomenon, experienced mostly as positive or neutral. They are associated with decreases in cognitive fusion from before to after 5-MeO-DMT use.

Keywords: 5-MeO-DMT, reactivation, psychological insight, cognitive fusion, ego-dissolution.

The Current Study

Recent decades have seen a resurgence of interest in investigating the use of psychedelic substances as mental health treatments. Research to date is promising; psilocybin, the most extensively investigated of the psychedelics, has been reported efficacious for various psychiatric disorders, including treatment-resistant depression (Carhart-Harris, Bolstridge, et al., 2018; Carhart-Harris et al., 2016; Carhart-Harris et al., 2017; Goodwin et al., 2022), major depressive disorder (Carhart-Harris et al., 2021; Davis, Barrett, May, et al., 2021; Gukasyan et al., 2022; Raison et al., 2023; Von Rotz et al., 2023), and substance use disorders (Bogenschutz et al., 2015; Bogenschutz et al., 2018; Bogenschutz et al., 2022; Garcia-Romeu et al., 2014; Johnson et al., 2014; Johnson et al., 2017; Noorani et al., 2018).

Over the past 10 years, another psychedelic, 5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) has gained significant interest as a potentially valuable mental health tool. 5-MeO-DMT is a short-acting, naturally occurring classic psychedelic substance belonging to the tryptamine family. It is found in several plant species such as *Anadenanthera peregrina* and *Virola theiodora* (Furst, 1976; Torres & Repke, 2006). Additionally, it is present in the defense secretions of the Sonoran Desert toad, *Incilius alvarius* (formerly *Bufo alvarius*) (Ermakova et al., 2022; Uthaug et al., 2019; Weil & Davis, 1994) and can be synthesized in laboratory settings (Morris, 2021; Sherwood et al., 2020).

Epidemiological data (Davis et al., 2018) and anecdotal reports from online forums (e.g., https://forums.5meodmt.org/) indicate that 5-MeO-DMT use is associated with a complex and understudied phenomenon called “reactivation.” Reactivation refers to a subjective experience where a person feels like they are reexperiencing some aspect of their acute 5-MeO-DMT dosing experience, which can occur days, weeks, or months after using 5-MeO-DMT. In this sense,

reactivations are similar to the 1960s term “flashback,” which was defined as “a reexperiencing of certain elements of the drug induced state after the drug’s effects have worn off” (Heaton & Victor, 1976; Matefy & Krall, 1974). However, unlike flashbacks, which have historically been perceived negatively and as intrusive or distressing, reactivations associated with 5-MeO-DMT can include positive and neutral experiences and are often viewed as part of the ongoing therapeutic process (Tap, 2024).

In the present study, we build on prior research that explored the reactivation phenomenon among two samples of English-speaking individuals (Ortiz Bernal et al., 2022) by investigating the prevalence, predictors, and emotional valence of reactivations in a sample of Spanish-speaking people. This is a significant endeavor, given that psychedelic studies to date are limited by the fact that they have been conducted primarily among White, English-speaking samples, with only 4.1% of participants being Black or Hispanic (Michaels et al., 2018). There has not been sufficient comparison between groups regarding patterns of naturalistic (i.e., non-clinical) use and impact on general well-being (Neitzke-Spruill, 2019). This lack of diversity may limit the generalizability of findings to minority populations, and hence, it is important to evaluate the impact of psychedelic use among diverse populations. Increasing participation of diverse populations is a critical area of psychedelic research, with ongoing efforts to address this gap (George et al., 2019; Thrul & Garcia-Romeu, 2021; Williams et al., 2023; Williams & Labate, 2019).

Motivation for using psychedelics has been shown to vary among ethnic groups (Rigg, 2017), and these motivations can predict different outcomes accordingly (Neitzke-Spruill, 2019). For example, Rigg (2017) found that African Americans who reported using the drug 3,4-methylenedioxymethamphetamine (MDMA) indicated their motivation was for altering the

effects of other drugs or for enhancing sexual pleasure, which differ from the introspection and self-enlightenment motivations often reported by White users (Rigg, 2017; Rigg, 2018).

Given the critical need for diversity in psychedelic research (Thrul & Garcia-Romeu, 2021; Williams & Labate, 2019) it is important to explore cultural differences in the use of psychedelics. There is growing interest in 5-MeO-DMT as a potential commercially available mental health tool (Aday et al., 2023). Therefore, it is relevant to assess the prevalence rates, predictors, and emotional valence of reactivation, as well as compare the motivation for using 5-MeO-DMT between previous English-speaking samples (Ortiz Bernal et al., 2022) and our present sample of Spanish-speaking individuals from Mexico, Central and South America, and Europe.

Subjective Effects and Preliminary Findings from Naturalistic and Observational Studies

The acute effects of the 5-MeO-DMT altered-state experience are much shorter compared to most other psychedelics, on the order of 20 to 60 minutes, depending on the route of administration (i.e., vaporized, intramuscular injection, etc.) (Reckweg et al., 2022; Shen et al., 2010; Uthaug et al., 2020). The subjective experience induced by 5-MeO-DMT is often described as transcendent, involving elements of ego-dissolution (Ermakova et al., 2022; Germann, 2019). Ego-dissolution experiences are characterized by a reduction in the self-referential processing that is pervasive in normal waking consciousness, leading to a disruption of self-other-world boundaries, and giving way to feelings of unity with others, nature, and the world at large (Kałużna et al., 2022; Nour & Carhart-Harris, 2017).

Despite the reduced duration of acute effects, preliminary evidence from naturalistic, and observational studies suggests that 5-MeO-DMT can improve mood disorders and well-being, with findings comparable to psilocybin (Armstrong et al., 2023; Barsuglia et al., 2018; Davis,

Averill, et al., 2020; Davis et al., 2018; Mangini et al., 2022; Uthaug et al., 2019). A survey-based study on the epidemiology and patterns of 5-MeO-DMT use among English-speaking individuals showed that many respondents reported improvements in anxiety, depression, substance misuse, and post-traumatic stress disorder (PTSD) symptoms following 5-MeO-DMT use in naturalistic settings. Furthermore, in a subsample of the 5-MeO-DMT survey in which only synthetic 5-MeO-DMT was used, 80% of respondents reported unintended improvements in symptoms of anxiety and depression after use in a group ceremonial setting (Davis et al., 2019).

Two observational studies explored the efficacy of a psychedelic treatment program that administers 5-MeO-DMT alongside another psychedelic called ibogaine, to United States veterans with severe PTSD and traumatic brain injuries. These studies showed significant post-treatment increases in participants' reports of psychological flexibility (Davis, Averill, et al., 2020; Mangini et al., 2022), which refers to the ability to stay in contact with the present moment despite unpleasant thoughts, feelings, or bodily sensations, while choosing one's behaviors based on personal values (Hoffmann et al., 2019). The increases in psychological flexibility among veterans were found to correlate with large and significant reductions in symptoms of PTSD, suicidal ideation, and anxiety in one study (Davis, Barrett, et al., 2020) and with reductions in PTSD symptoms and alcohol misuse in the other (Mangini et al., 2022).

Psychological flexibility is a core concept that derives from Acceptance and Commitment Therapy (ACT), which is increasingly used as part of a supportive framework for psychedelic therapy preparation and integration sessions (Luoma, Davis, et al., 2020; Luoma et al., 2019; Sloshower et al., 2020; Watts et al., 2017; Watts & Luoma, 2020). In the ACT model, the goal of therapy is psychological flexibility, and it is achieved through six interrelated processes, one of which is called cognitive defusion (Harris, 2019). Cognitive defusion refers to the ability to

distance oneself from thoughts and memories, whereas cognitive fusion refers to a mental process whereby individuals become so entangled in their thinking patterns they can no longer separate themselves from their thoughts (Gillanders et al., 2014). Cognitive fusion has been reported to be a core factor in the formation and maintenance of many psychiatric disorders (Chen et al., 2023; Faustino et al., 2021), and high levels of cognitive fusion are correlated with anxiety and depression (Chen et al., 2023; Hitchcock et al., 2018; Thomas & Bardeen, 2020).

A recent study (Chapter 2 of this dissertation) found significant decreases in cognitive fusion levels from before-to-after 5-MeO-DMT use in naturalistic settings. Additionally, decreases in cognitive fusion were associated with the intensity of certain 5-MeO-DMT acute effects. Specifically, greater intensity of challenging experiences and greater ratings of psychological insight predicted decreases in cognitive fusion.

In line with this finding, the intensity of acute psychedelic effects has been found to predict long-term positive outcomes. For example, greater intensity of challenging experiences associated with psychedelic use has been shown to predict enduring increases in well-being (Carbonaro et al., 2016). Furthermore, recent studies have also shown that psychological insight associated with psychedelic experiences may be a robust predictor of long-term therapeutic effects (Davis, Barrett, et al., 2020; Davis, Xin, et al., 2021).

Based on the positive findings from the observational and naturalistic studies conducted to date, various synthetic 5-MeO-DMT formulations (e.g., intranasal, vaporized, intramuscular) are being investigated as potentially novel and effective mental health treatments for a variety of psychiatric disorders (Reckweg et al., 2022). A recently published clinical trial that assessed the safety and efficacy of vaporized 5-MeO-DMT in patients with treatment-resistant depression found that 5-MeO-DMT produced rapid antidepressant effects (as quickly as two hours post-

dosing) that were associated with full remission at the one week endpoint (Reckweg et al., 2023). A phase 1, placebo-controlled trial with an intranasal formulation of 5-MeO-DMT was also recently published, showing it was well tolerated in doses up to 12 mg. (Rucker et al., 2024).

As of July 17, 2024, the clinicaltrials.gov website lists 14 5-MeO-DMT trials that are either recently completed or currently recruiting. Ongoing studies include a trial for postpartum depression (Identifier: NCT05804708), two trials for treatment-resistant depression (Identifier: NCT05800860, Identifier: NCT05660642), and a trial for Bipolar Disorder II (Identifier: NCT05839509).

The Reactivation Phenomenon: Potential Boon or Barrier to 5-MeO-DMT Research and Therapy?

Ongoing research into 5-MeO-DMT's potential therapeutic applications is promising, as continued success in clinical trials could lead to its approval as a rapid, novel, safe, and effective mental health treatment. However, despite this encouraging progress, the association of 5-MeO-DMT use in naturalistic settings with reactivations, and our limited understanding of this phenomenon, could potentially hinder future research. Therefore, it is critically important to study reactivations among diverse populations to enhance our understanding and inform safe therapeutic practices. Reactivation refers to a complex and poorly understood phenomenon that is similar to flashbacks (Heaton, 1975; Heaton & Victor, 1976; Matefy & Krall, 1974). Previous studies have primarily examined this phenomenon in mostly White English-speakers (Ortiz Bernal et al., 2022). The present study aims to extend the understanding of reactivations to a Spanish-speaking population, providing insights into how cultural differences may influence the prevalence, predictors, and emotional valence of reactivations.

Two varieties of flashbacks are described in the DSM-5 under the diagnosis of Hallucinogen persisting perceptual disorder (HPPD): Type 1 and Type 2 (Halpern et al., 2018).

Type 1 is characterized by brief and benign re-experiencing of some felt sense of the acute psychedelic effects (i.e., stand-alone flashbacks), whereas Type 2 HPPD is more severe, with perceptual distortions causing disruptions to daily life for an extended period of time (Lerner et al., 2014).

A prior study by our team conducted an initial exploratory analysis of the prevalence, predictors, and emotional valence of reactivation phenomena in two subsamples of English-speaking individuals (Ortiz Bernal et al., 2022). One of the subsamples used 5-MeO-DMT in a structured ceremonial group context (Davis et al., 2019), and the other subsample consisted of individuals from the general population who reported using 5-MeO-DMT in non-structured settings (e.g., their home/apartment or a friend's house). Results showed a statistically significant difference in the rate of reactivations reported between the study subsamples (73% in the structured group versus 27% in the general population), and that nearly all survey respondents indicated their reactivation events were perceived as positive/neutral experiences (96% in the structured group and 93% in the general population). One possible factor explaining the difference in reactivation rates between the subsamples is dosage. In the structured group subsample, carefully weighted doses are administered reliably based on each individual's known sensitivities and prior experience, whereas in the general population (Davis et al., 2019), dosage varies more widely and may not be carefully weighted given the unstructured context. However, specific and reliable dosage information is not available to substantiate this idea. In general terms, findings from that initial study suggest reactivations are akin to Type 1 HPPD, but some anecdotal reports also suggest there are instances where they may include Type 2 features.

The strongest predictor of reactivations in the prior study was gender, with women being almost twice as likely to report reactivation as men (Ortiz Bernal et al., 2022). Additionally,

increased amount of time planned ahead for a 5-MeO-DMT dose and greater meaningfulness attributed to the experience were also significantly associated, with those participants reporting higher likelihood of reactivation events.

In terms of emotional valence, that is whether a person perceived reactivation events as a positive, neutral, or negative experience, older age at the time of the 5-MeO-DMT experience was associated with lower likelihood of reporting positive/neutral emotional valence of reactivation events, whereas taking 5-MeO-DMT in the structured, ceremonial setting was associated with a higher likelihood of positive/neutral emotional valence of reactivation events.

Interestingly, although reactivations associated with the use of 5-MeO-DMT in naturalistic settings are a well-documented phenomenon in online support groups and forums (e.g., https://forums.5meodmt.org/), besides the study described above, there are only two other studies in the scientific literature address reactivations (Dourron et al., 2023; Uthaug et al., 2020). One of the studies, by Uthaug and colleagues, compared rates of reactivation based on 5-MeO-DMT's route of administration (vaporization versus intramuscular injection). They found significantly higher reactivation rates in the vaporization group (69%) compared to the intramuscular injection group (21%) (Uthaug et al., 2020). One possible explanation for this difference is that redosing (e.g. taking a second dose within the same dosing session) occurred more frequently in the vaporization group, meaning participants received higher and more frequent doses than the intramuscular group.

Dourron et al. (2023) hypothesize that the reactivation phenomenon may be due to the drug's potential to induce temporary epileptiform activity, particularly in the temporal lobes. However, the hypothesis is primarily based on observational and anecdotal evidence, and no electroencephalography (EEG) or imaging studies have been completed to date to provide direct

empirical evidence for epileptiform activity following 5-MeO-DMT use. Without such studies, the exact mechanisms underlying reactivations and their potential link to epileptiform activity remain unclear.

As psychedelic science and mainstream mental health practitioners continue to bring compounds like 5-MeO-DMT to the forefront of mental health treatments, it is becoming increasingly important to address potential adverse reactions. Simultaneously, identifying possible therapeutic opportunities is crucial for developing optimal models of drug delivery and patient care in this emerging field. In light of this, understanding reactivations is a critical endeavor that needs to be undertaken because: 1) although historically classified as adverse effects, they may represent more nuanced phenomena that deserve better characterization; and 2) a need exists to communicate the prevalence, predictors, and emotional valence of these experiences in developing, testing, and administering treatments using 5-MeO-DMT.

Aims of The Present Study

The present study aims to contribute to the process of diversifying samples used in naturalistic psychedelic studies by examining the prevalence, predictors, and emotional valence of reactivation phenomena among a sample of Spanish-speaking individuals from Mexico and a few other countries. Previous research has shown that the intensity of certain types of acute effects are associated with long-term positive impact on mental health (Carbonaro et al., 2016; Davis, Barrett, et al., 2020; Davis, Xin, et al., 2021; Uthaug et al., 2019). Building on these findings, in the present study, we set out to examine the associations between acute 5-MeO-DMT effects (i.e., ego dissolution, challenging experiences, and psychological insight), reactivation events, and their attributed emotional valence. We further investigate if reactivation events are

associated with decreases in cognitive fusion from before-to-after 5-MeO-DMT use, and with enduring positive effects related to the meaningfulness attributed to the 5-MeO-DMT.

Method

Measure Translation

All measures included in the study and described below were translated using the forward-and-back translation technique as described previously (Davis et al., 2023). Briefly, translations were performed by team members fluent in English and native Spanish speakers. The survey was initially created in English and then translated into Spanish by a team member. Subsequently, this Spanish version was back-translated into English by another team member. The back-translation was compared to the original English questionnaires to ensure that the translation process had not altered the meaning. In the event of discrepancies or confusion, individual phrases were retranslated to ensure appropriate clarity and meaning. This rigorous translation process aimed to maintain the integrity of the questionnaires and ensure the suitability for Spanish-speaking participants.

Study Procedure and Flow

Data for the present study were collected as part of a larger, anonymous, online-based cross-sectional survey of Spanish-speaking individuals who reported having used a psychedelic substance at least once. Respondents were asked to complete the survey based on a memorable experience with either mescaline/peyote/San Pedro, psilocybin/psilocybin mushrooms, LSD, or 5-MeO-DMT. The present study is limited to the sub-sample of respondents who selected 5-MeO-DMT.

Respondents were recruited from June 2020 to June 2021 through online advertisements posted on relevant websites including www.drugs-forum.com and www.bluelight.org, email

invitations, online flyers, and word of mouth. Interested individuals were referred to an electronic copy of the official survey recruitment flyer. After clicking the link for the secure, anonymous survey (hosted on www.qualtrics.com), each respondent was presented with a statement regarding the purpose of the study, and the informed consent document detailing inclusion criteria (i.e., being at least 18 years old, able to read, write, and speak Spanish fluently, having taken 5-MeO-DMT at least once). After completing the consent document, respondents completed the survey questions based on their most memorable experience with 5-MeO-DMT. A total of 379 people consented to complete the 5-MeO-DMT survey. However, of these, 289 did not even start the survey and were not included in the analyses, thus yielding a total sample of 90 respondents. No identifying information was collected. No incentives or compensation were offered. This study was deemed exempt from IRB review at the University of Wisconsin-Madison.

Measures

This study included some exploratory background questions to understand the context in which Spanish-speaking individuals used 5-MeO-DMT, such as where they obtained the drug (e.g. purchased it online/from a friend/stranger, received it in a ceremony, gifted/other) and who administered it (e.g., self-administered, shamanic practitioner/church leader, friend/peer sitter/treatment center/other). Given the general lack of information about reactivations in the scientific literature, we were also interested in assessing the timeframe in which reactivations tend to occur following 5-MeO-DMT use. We administered the question “How long after your experience with 5-MeO-DMT did the reactivation happen?” (e.g., some days after, around one or two weeks after, around three or four weeks after, after a month). Further, given the common anecdotal reports of reactivations in online forums, we were also interested in examining whether

people were aware of the possibility of reactivations taking place before they used 5-MeO-DMT (e.g., yes, no).

Primary and secondary outcome measures for the present study were prevalence of reactivation events and emotional valence of these events when reported. To assess these outcomes, a Spanish translation of the following question was administered: “Have you had a spontaneous re-experiencing or reactivation of a past 5-MeO-DMT experience after using the drug (e.g., a flashback or a feeling as though your 5-MeO-DMT experience is happening again?” (e.g., yes, no). Those respondents who answered “yes” were further asked: “Was it a negative, neutral, or positive experience?” A dichotomous variable was created, indicating whether the experience was positive versus neutral or negative.

Predictors Included Based on Prior Research

Given the strong effects of gender on reactivation events reported previously and that the amount of time planned ahead in preparation for a 5-MeO-DMT experience was associated with higher likelihood of reactivation experiences (Ortiz Bernal et al., 2022), predictors of reactivation explored in this study were gender (e.g., male, female), and amount of time planned ahead for a 5-MeO-DMT experience (e.g., no plan or a few days, one week or more). Although education is a predictor that was assessed in the previous reactivation study, in the present one, it was not associated with the primary nor secondary outcome, and hence, was not included in the analyses included herein. Additionally, given that in the present study we only had one sample, as opposed to two separate subsamples like in the previous study (Ortiz Bernal et al., 2022), context of use was not assessed.

5-MeO-DMT Acute Psychedelic Effects

Ego-Dissolution Effects. Because the 5-MeO-DMT altered state experience is often described in terms of its potent ego dissolving effects (Ermakova et al., 2022), we included the Ego-Dissolution Inventory as a measure of acute effects. The Ego-Dissolution Inventory is an 8-item self-report scale that assesses the degree to which individuals lose the capacity for self-referential processing during a psychedelic experience. Respondents were asked to think back to their memorable 5-MeO-DMT dose and to rate the intensity with which they experienced each of the items at any point during their experience. Sample items include statements such as "I experienced a disintegration of my 'self' or ego," and " I felt at one with the universe." (Nour et al., 2016). The scale is rated using a 6-point Likert scale with response options ranging from "No, not at all" to "Extreme." The total score is the mean of the eight items. The higher the total score, the greater the intensity of the ego dissolution experience. This measure has been found to have good construct validity (Nour et al., 2016). Internal consistency in our sample was good (α = .89).

Challenging Experiences. To assess challenging experiences in relation to 5-MeO-DMT use, we included the Challenging Experiences Questionnaire. This 26-item questionnaire assesses difficult experiences related to acute psychedelic effects, including feelings of grief, fear, insanity, death, isolation, physical distress, and paranoia (Barrett et al., 2016). Respondents were asked to think back to their memorable 5-MeO-DMT dose and to rate the intensity with which they had several experiences. Sample items of this scale include "Feeling my heart beating" and *"Feeling my body shake/tremble."* This scale is scored using a 6-point Likert scale ranging from "None, not at all" to "Extreme." Previous studies have found this scale has excellent internal consistency (α = .97) (Davis, Xin, et al., 2021), which was also reflected in our sample (α = .93).

Psychological Insight Effects. Psychological insight associated with psychedelic experiences is emerging as an important predictor of long-term therapeutic effects. For this reason, 5-MeO-DMT acute effects were also examined using the Psychological Insight Questionnaire. This recently validated 23-item scale was specifically designed to assess insight experiences that may occur in association with psychedelic use. Insight experiences can be related to emotions, beliefs, memories, and relationships (Davis, Barrett, So, et al., 2021). Respondents were asked to think back to their 5-MeO-DMT experience and to rate the degree to which they experienced each of the scale items. Scale items include statements such as "Discovered I could explore uncomfortable or painful feelings I previously avoided," and "Realized how current feelings or perceptions are related to events from my past." The scale is scored using a 6-point Likert-type scale ranging from "None; not at all" to "Extreme." Davis et al. (2020) found that this scale had excellent internal reliability ($\alpha = .93$), as so did Moreton et al. (2022) ($\alpha = .97$), which was also reflected in the present study ($\alpha = .94$).

Beliefs About Persisting Effects of 5-MeO-DMT. A single item from the Persisting Effects Questionnaire was included in this study (Griffiths et al., 2008; Griffiths et al., 2011; Griffiths et al., 2006). This item asked respondents to think back to the memorable experience they had when they ingested 5-MeO-DMT and to answer the following question: "How personally meaningful was your experience and your contemplation of that experience?" This item is scored using a 7-point scale ranging from "No more than routine, everyday experiences" to "The single most meaningful experience of my life."

Changes in Cognitive Fusion. Cognitive fusion levels from before-to-after 5-MeO-DMT use were measured using the Cognitive Fusion Questionnaire, a 7-item scale that assesses excessive attachment to the literal content of thoughts and rigid cognitions, which render

psychological flexibility difficult to cultivate (Gillanders et al., 2014). Respondents were asked to indicate to what extent each statement was true for them before and after their 5-MeO-DMT experience. Sample items from this scale are “My thoughts cause me distress or emotional pain” and “I get so caught up in my thoughts that I am unable to do the things that I most want to do.” Questions of this scale are recorded on a 7-point scale ranging from “Never true” to “Always true”. Respondents completed this measure twice: once with respect to before their memorable 5-MeO-DMT experience, and once with respect to after their memorable 5-MeO-DMT experience. Higher scores indicate greater cognitive fusion. We examined changes in cognitive fusion by calculating a mean change score. The change score in cognitive fusion from before to after 5-MeO-DMT was calculated by subtracting the mean cognitive fusion *before* score from the mean cognitive fusion *after* score for each respondent. Decreases in cognitive fusion indicate improvements. There is good preliminary evidence of the questionnaire’s factor structure, reliability, temporal stability, validity, discriminant validity, and sensitivity to treatment effects (Gillanders et al., 2014). The internal consistency of this scale in our sample was excellent (α = .93 for before and α = .90 for after).

Demographics

Respondents self-reported their demographic information including age, gender, sexual orientation, education level, and country of residence.

Plan for Analysis

First, descriptive statistics for demographic and background characteristics for all study variables were tabulated. Second, cross-tabulations were computed to explore the rate of self-reported reactivation events and the emotional valence associated with them. Other descriptive exploratory data analyzed included the timeframe in which reactivations occurred following 5-

MeO-DMT use, as well as whether or not respondents were aware of the possibility of reactivations prior to dose. In the third step, the primary outcome variable, reactivation, was regressed first on each individual predictor variable to assess bivariate effects, and then in a multivariable logistic regression model to examine unique effects.

Lastly, the secondary outcome variable of emotional valence (positive versus neutral/negative) was also regressed first on each individual predictor to examine bivariate relationships, then in a multivariable logistic regression to examine unique effects. The same predictors as in the reactivation analyses were examined here, except for gender and the item related to meaningfulness. These two predictors were omitted from the emotional valence analyses given the reduced statistical power for this set of analyses due to the fact that of the 90 respondents in the full sample, only 62 were further asked about the emotional valence of reactivations (those that said they had had a reactivation only).

To simplify the interpretation of logistic regression results for changes in cognitive fusion from before-to-after 5-MeO-DMT use (where decreases in cognitive fusion indicate improvement), we created a reversed score variable. In this reversed score, higher values reflect greater reductions in cognitive fusion, signifying improvement. Additionally, the measures of acute effects (ego-dissolution, challenging experiences, and psychological insight) were centered to aid in interpretation of both bivariate and multivariable logistic regression analyses.

Results

Descriptive Data

Table 1 displays demographic and 5-MeO-DMT use characteristics of the sample. The average age of respondents was 38.89 years (*SD* = 11.57), with 67% being male. Regarding education, 46% had at least some college education, 35% had an associate or bachelor's degree,

and 19% had an advanced degree. Fifty three percent of respondents indicated México as their country of origin, and the remainder reported being from various South American, Central American and European countries, and the United States. Regarding the source of 5-MeO-DMT, 11% purchased it online or from a friend/stranger, 71% received it at a ceremony, and 18% indicated it was gifted or obtained through other means. In terms of administration, 18% self-administered the substance, 62% had it administered by a shamanic practitioner or church leader, and 20% by a friend, peer sitter, at a treatment center, or other.

Exploratory Questions, Prevalence Rates and Emotional Valence

In response to the exploratory background question "Were you aware of the possibility of having reactivations as a result of using 5-MeO-DMT before using the substance?" the sample was split almost equally: 52% did not know, and 48% were aware beforehand. Regarding the question, "How long after your experience with 5-MeO-DMT did the reactivation happen?", respondents reported a wide range of timeframes: 26 % indicated it happened some days after, 24% said around one or two weeks, 26% of respondents reported around three or four weeks, and 24% stated it occurred after one month In terms of prevalence rates, 69% of respondent reported reactivations. Of these, 3% described it as a negative experience, 16% rated it as neutral, and 81% indicated it was positive.

Logistic Regression Analyses: Reactivation

Table 2 displays the results of logistic regression analyses for reactivation events. Bivariate analyses revealed several factors associated with increased odds of reporting reactivations: longer planning time (OR = 3.96, CI: 1.50 – 10.40, p = .005), higher intensity of ego dissolution effects (OR = 1.58, CI: 1.04 – 2.39, p = .032), greater psychological insight effects (OR = 1.50, CI: 1.02 – 2.22, p = .037), greater meaningfulness of the 5-MeO-DMT

experience (OR = 1.59, CI: 1.03 – 2.47, p = .038), and greater mean changes in cognitive fusion from before-to-after 5-MeO-DMT use (OR = 2.10, CI: 1.33 – 3.33, p = .002). In the multivariable model, controlling for all other variables, two factors emerged as significant unique predictors of reactivations: longer time planned ahead (OR = 3.03, CI: 1.04 – 8.88, p = .043), and greater mean changes in cognitive fusion (OR = 1.76, CI: 1.02 – 3.05, p = .042).

Logistic Regression Analyses: Emotional Valence

Table 3 displays results of logistic regression analyses for the emotional valence of reactivation events. In the bivariate analyses challenging effects were associated with a decreased likelihood of reporting a positive reactivation event (OR = 0.52, CI: 0.29 – 0.96, p = .037), and psychological insight effects were significantly associated with an increased likelihood of reporting a positive reactivation experience (OR = 1.94, CI: 1.06 – 3.54, p = .032). Both of these predictors remained significant in the multivariable model; challenging effects (OR=0.43, CI: 0.20 - 0.95, p = 0.037); psychological insight effects (OR = 2.43, CI; 1.08 – 5.45, p = .032), controlling for the effects of all other variables.

Discussion

The present retrospective cross-sectional study examined the prevalence rates, predictors, and emotional valence of a complex phenomenon associated with the use of 5-MeO-DMT among a sample of Spanish-speaking people from Mexico and other Spanish-Speaking countries. Termed reactivation, this poorly characterized subjective experience appears to be a common occurrence among those who use 5-MeO-DMT in naturalistic settings. Exploratory data suggest that the timeframe in which reactivations occur following 5-MeO-DMT use is highly variable, ranging from within a few days post dose, to after one month after the dose. It is notable that approximately half of the respondents were aware of the possibility of reactivations before using

5-MeO-DMT, suggesting that this is a fairly common and anticipated phenomenon that does not deter individuals from using the substance.

Prevalence Rate and Contextual Considerations

The prevalence rate of 69% among this sample of Spanish-speaking individuals is consistent with the prevalence rates reported for the structured group English-speaking sample from our prior study (Ortiz Bernal et al., 2022). As noted on Table 1, 71% of respondents said the 5-MeO-DMT they used had been provided at a ceremony, and 62% of respondents indicated they had been administered the 5-MeO-DMT dose by a shamanic practitioner. Both of these characteristics are somewhat consistent with the structured ceremonial group context; thus, it makes sense that prevalence rates in this sample of Spanish-speaking individuals is more akin to the structured group context (73%) than the general population context (27%) from the prior study (Ortiz Bernal et al., 2022). Future research should focus on exploring the specific factors that contribute to higher reactivation rates in different contexts.

Nearly all respondents (97%) who reported a reactivation event in the present study perceived it as a neutral or positive experience. This is consistent with findings of our prior study, which showed that 96% of the English-speaking respondents in the structured group subsample reported reactivations as neutral or positive, and 93% of English-speaking respondents from the general population subsample also ascribed a neutral or positive emotional valence to their reactivation events.

In the prior paper, we posited that this pattern of results suggests that the reactivation phenomenon might be conceptualized not as an adverse effect, but as a neutral or positive byproduct of the 5-MeO-DMT experience. And further, that it may even be possible that such events contribute to the therapeutic effects that have been documented in the literature to date (Davis, Averill, et al., 2020; Davis et al., 2018; Mangini et al., 2022; Ortiz Bernal et al., 2022;

Ragnhildstveit et al., 2023; Uthaug et al., 2019). The high percentage of respondents in both studies endorsing their reactivation as a positive or neural experience aligns with the conceptualization of reactivations as potentially helpful and therapeutic rather than a clinical hindrance, However, more research is needed to better characterize the phenomenon and understand the factors that may lead to a reactivation being perceived as negative. Although only 3% of respondents in the present study reported a negative reactivation, consistent with the prior finding of 4% and 7% in the structured subsample and general population subsamples respectively (Ortiz Bernal et al., 2022), it is crucial to investigate what may contribute to such outcomes. Future studies should also study the incidence of reactivations prospectively in a clinical population and how reactivations relate to clinical response.

Future studies should focus on identifying specific triggers or conditions that result in negative reactivations, such as individual differences in psychological resilience, the context of the 5-MeO-DMT experience, or pre-existing mental health conditions. Additionally, qualitative research involving in-depth interviews with individuals who have experienced negative reactivations could provide valuable insights into the subjective aspects of these experiences.

Predictors of Reactivation Events

Unlike our prior study, which showed women were about twice as likely to report reactivation events as men (OR = 1.82, CI: 1.11–2.99, p = .016), the present study did not show this gender difference in reactivation. That this gender bias was not reproduced in the present Spanish-speaking sample could be attributed to several factors. Cultural differences in gender roles and expectations could influence the willingness of women to report such experiences (Schmitz et al., 2004). In some Spanish-speaking cultures, traditional gender norms might discourage women from openly discussing their psychological experiences or troubles (e.g. the

Latino value of "Marianismo" dictates women ought to endure suffering with dignity) (Abdullah & Brown, 2011). Furthermore, the methodology and context of the studies, including recruitment strategies could contribute to these differing outcomes. Whereas the subsample of the structured group in Ortiz Bernal et al. (2022) was recruited via an email distribution list of individuals that took 5-MeO-DMT within that ceremonial context regularly (Davis et al., 2019), recruitment for the present study took place mainly via the online equivalent of word of mouth, Facebook posts, and posts on other relevant Spanish websites. These findings highlight the importance of considering cultural context when studying psychedelic experiences and underscore the value of including diverse populations in research to enhance our understanding of these phenomena.

On the other hand, consistent with our previous findings, the amount of time planned ahead for a 5-MeO-DMT dose was significantly associated with increased likelihood of reactivation events in the present study. Those who planned ahead for at least a week were almost four times more likely to report reactivations in the bivariate analyses, and three times more likely in the multivariable model.

That the longer a respondent planned ahead for their 5-MeO-DMT experience was positively associated with reactivation both in the present study and the previous one could be posited to be indicative of an intentional self-directed behavior process that is facilitated or catalyzed by the intentional use of 5-MeO-DMT (Ortiz Bernal et al., 2022; Ragnhildstveit et al., 2023). In this sense, perhaps reactivations can be conceptualized as transient after-effects that favor and support change in the direction of the desired target behavior (i.e., the specific intention the individual sets for their 5-MeO-DMT experience), facilitating processes of self-directed neuroplasticity (Hanson, 2013, 2018, 2009).

Recent research using cerebral organoids has provided compelling evidence for the neuroplasticity-enhancing effects of 5-MeO-DMT at the molecular level. Dakic et al. (2017) demonstrated that a single 24-hour treatment with 5-MeO-DMT induced significant changes in the expression of nearly 1,000 proteins in these cerebral organoids. Many of these proteins were associated with long-term potentiation, learning, memory, and dendritic spine formation, suggesting a potential mechanism for neuroplasticity. The study also observed increases in proteins involved in neuritogenesis and decreases in inflammatory markers (Dakic et al., 2017). These changes suggest that 5-MeO-DMT may promote structural and functional neuroplasticity, potentially facilitating brain remodeling, and enhancing overall well-being.

Given this understanding of psychedelics, including 5-MeO-DMT, as potent inducers of neuroplasticity, reactivations that occur days, weeks or even months after a single 5-MeO-DMT dose could be conceptualized as elements that support an unfolding process of self-directed positive behavioral change. When individuals plan ahead for their 5-MeO-DMT dose, setting specific intentions or therapeutic objectives, they may be creating a foundation for neuroplastic changes that enhance the potential benefits of the experience. Although extensive preparations are also made for other psychedelics, the reactivations seen with 5-MeO-DMT may be hypothesized to uniquely reflect ongoing neuroplastic processes initiated by the drug. The neuroplasticity induced by 5-MeO-DMT may extend beyond the acute experience, potentially influencing the occurrence of reactivations. Future studies should investigate this hypothesis by examining the long-term neuroplastic effects of 5-MeO-DMT, utilizing neuroimaging and molecular techniques to explore the potential link between neuroplasticity and reactivations, and comparing these effects with those of other psychedelics. Additionally, these studies should also assess whether the occurrence of reactivations predicts improved clinical outcomes compared to

those who do not report reactivations, guiding the development of personalized treatment protocols and enhancing therapeutic efficacy.

It could be argued, and empirically tested in upcoming studies, that when individuals approach their 5-MeO-DMT experience with clear intentions, they may gain psychological insights about their lives and experience a reduction in cognitive fusion. Subsequent reactivations that remind them of these intentions and insights could serve as reinforcers of self-directed behavioral change and neuroplasticity. This cycle of intention, insight, and reinforcement through reactivations may contribute to sustained personal growth and clinical improvements, in service of the intention that was identified prior to 5-MeO-DMT dosing (Ragnhildstveit et al., 2023). However, this raises the question of why reactivations might not occur as frequently in individuals who did not set intentions. One hypothesis is that setting clear intentions may prime the brain to be more receptive to reactivations by creating a specific cognitive and emotional framework that facilitates the recall and integration of the psychedelic experience. Future studies should investigate how intention-setting influences the frequency and impact of reactivations, and assess the mechanisms through which reactivations may potentially support ongoing therapeutic processes.

Intensity of Acute Effects and Likelihood of Reactivations

Greater ratings of ego-dissolution effects were significantly associated with a higher likelihood of reporting reactivation events in the bivariate analysis. The intense ego-dissolution experience that 5-MeO-DMT induces can lead to a breakdown of usual cognitive and emotional boundaries, which might not be fully processed during the initial experience. Reactivations could occur as the brain continues to integrate these experiences. The intensity of ego-dissolution effects may facilitate reactivations by deeply imprinting the 5-MeO-DMT experience in the

individual's consciousness, making it more likely for these experiences to resurface. These reactivations can serve as reinforcing events that help sustain and integrate the positive changes initiated and catalyzed by the intentional use of 5-MeO-DMT. This aligns with previous findings that greater ego-dissolution is associated with enduring positive changes in well-being, life satisfaction, and attitudes about self, nature, and the world (Uthaug et al., 2019; Uthaug et al., 2018).

Future research could aim to further explore the connection between ego-dissolution, reactivations, and their impact on well-being. Prospective longitudinal studies are needed to track participants over time, assessing changes in well-being, life satisfaction, and other persisting effects. These studies should measure ego-dissolution and other acute effects immediately after the 5-MeO-DMT dosing session and include regular follow-up visits to assess the incidence and phenomenology of reactivations that may occur in the days to months following dosing.

Psychological insight effects were also positively associated with a higher likelihood of reactivation events in the bivariate analyses. As mentioned previously, psychological insight is emerging as a robust predictor of psychedelics' therapeutic effects (Davis, Barrett, et al., 2020; Davis, Xin, et al., 2021). The finding that greater rating of psychological insight gleaned from the 5-MeO-DMT experience was associated with a higher likelihood of reactivations suggests that reactivations might serve as reflective moments, allowing individuals to process and integrate their insights over time. This repeated processing could reinforce the therapeutic gains, leading to sustained improvements in mental health.

Decreases in Cognitive Fusion and Meaningfulness of the 5-MeO-DMT Experience

Additionally, the association between decreases in cognitive fusion and reactivations both in the bivariate and the multivariable logistic regression suggest that these events may help individuals maintain a more flexible and adaptive cognitive style, further supporting long-term

well-being (Bramwell & Richardson, 2018). Cognitive fusion, that is, overidentification with one's thoughts such that they are taken to accurately represent reality, as conceptualized in the ACT model, is posited to be the overarching pathological process underlying mental health concerns (Harris, 2019). Given the present study's finding that psychological insight and decreases in cognitive fusion from before-to-after 5-MeO-DMT are significant predictors of reactivations, future research should explore the mechanisms by which these factors associated with reactivations may contribute to lasting therapeutic outcomes.

Greater meaningfulness attributed to the 5-MeO-DMT experience in the present study was associated with higher likelihood of reactivation events, consistent with findings from our prior study (Ortiz Bernal et al., 2022), though this was observed only in the bivariate analyses in the present study. Nevertheless, the fact that greater meaningfulness has been predictive of reactivation events across three different samples to date supports the idea that reactivations may reinforce and support processes of personally meaningful positive change (Hanson, 2009; Klein et al., 2019).

The association between meaningfulness and reactivations also aligns with the concept of cognitive salience in memory formation and retrieval. Experiences that are perceived as highly meaningful are more likely to be deeply encoded and subsequently recalled (Talarico & Rubin, 2003). Reactivations could be a result of these deeply encoded memories being spontaneously recalled. This heightened salience of the 5-MeO-DMT experience may facilitate the integration of insights gained during the acute experience into everyday life through reactivations.

Additionally, this finding supports the "*pivotal mental states*" construct introduced by Brower and Carhart-Harris (2021), which proposes that psychedelics can induce highly meaningful states, highly dependent on context, that serve as reference point for future cognition

and behavior. The authors posit that these pivotal mental states can lead to rapid and lasting changes in beliefs, behaviors, and overall well-being, or on the other hand, to psychopathology (Brouwer & Carhart-Harris, 2021). In this context, reactivations may serve as spontaneous revisitations of these pivotal states, potentially reinforcing and extending their impact over time. This process could be understood as a form of experiential learning, where the brain repeatedly "rehearses" and reinforces the most salient aspect of the psychedelic experience through reactivations.

However, without neuroimaging data and additional psychological assessments to substantiate these mechanisms, all ideas regarding the exact nature and function of reactivations remains speculative. Ongoing and future research employing neuroimaging techniques such as functional magnetic resonance imaging (fMRI) or EEG, will provide critical insights into the neural underpinnings of reactivations.

Emotional Valence of Reactivations

In terms of the emotional valence of reactivations, the present study suggests that greater challenging effects were associated with decreased likelihood of a person perceiving reactivations as positive, while greater psychological insight effects were associated with increased likelihood of positive emotional valence. This highlights the importance of the context in which 5-MeO-DMT is used or administered, emphasizing the need to reduce potential challenging effects and enhance therapeutic benefits through a well-designed, comprehensive preparation process.

As in our previous reactivation study, the present study findings suggests reactivations are a fairly common phenomenon akin to HPPD Type 1, which may not necessarily be construed as adverse effects. However, it is important to acknowledge anecdotal reports from individuals who struggle with reactivations for extended periods of time after a high-dose toad-derived 5-

MeO-DMT, as reported in online forums (i.e., https://forums.5meodmt.org/). These cases may be indicative of HPPD Type 2. A small percentage of individuals in these online support forums do report negative experiences, including anxiety and insomnia, due to reactivations happening at night when they are falling asleep.

While reactivations associated with 5-MeO-DMT are similar to HPPD Type 1 in terms of their frequency and generally non-bothersome nature, they often differ in their phenomenology. Reactivations may include a broader range of emotional valence, including positive and neutral experiences, which are less commonly reported in HPPD Type 2 cases linked to other psychedelics like LSD. Many more studies, with longitudinal mixed methods designs and larger sample sizes, are needed to better characterize the reactivation phenomenon, understand its precipitating triggers, and assess how it compares to HPPD Type 1 and 2.

Given the interest that exists to develop 5-MeO-DMT as a mental health treatment, it is imperative we identify risk factors for negative reactivation experiences so that we may aim to prevent such challenging outcomes. It is also important to explore how this seemingly common phenomenon may be harnessed to optimize treatment outcomes and support continued long-term positive change processes. Current and future clinical trials with 5-MeO-DMT could greatly help expand our understanding of the reactivation phenomenon by collecting qualitative accounts of the phenomenology of the experience, and details about precipitating factors when they occur.

Furthermore, it is essential to determine whether sub-acute periods of negative reactivations might predict ultimate therapeutic benefit. While we do not yet know enough about these reactivations, studying their long-term impacts could reveal whether initial negative experiences are linked to greater overall improvements.

Ongoing and future trials can also inform future delivery of care processes if and when 5-MeO-DMT is granted approval as a treatment by the Food and Drug Administration (FDA). By systematically documenting the contexts and conditions under which reactivations occur, these studies can help develop best practices for reactivation-informed preparation, dosing, and integration sessions. Additionally, understanding individual differences in response to 5-MeO-DMT can guide personalized treatment plans and individualized dose regimens, optimizing conditions for clinically significant improvements, behavioral changes, and increases in well-being.

It is essential to incorporate information about the potential for reactivations into the informed consent process for clinical trial participants, and address throughout the preparation sessions leading to a dosing. Providing clear, comprehensive details about reactivations – including their likelihood, possible duration, and range of emotional experiences – ensures that participants are fully informed about what they might encounter. This transparency not only adheres to ethical research standards but also helps participants make well-informed decisions about their involvement and prepares them for potential post-session experiences.

Examining Alternative Explanations for Reactivation Phenomena

As mentioned in the Introduction, Dourron et al. (2023) have proposed a potential link between reactivations and temporal lobe seizures. But as previously noted, this hypothesis is based on anecdotal evidence and lacks support from EEG or neuroimaging studies. Several factors suggest alternative explanations may be more plausible. Unlike seizures, reactivations are often reported as meaningful, insightful experiences that individuals can engage with or disengage from at will. Although some seizures, including brief temporal lobe seizures, can last from 30 seconds to 5 minutes and longer ones up to 30 minutes (Chowdhury et al., 2021),

reactivations are typically shorter and are often triggered by specific stimuli related to the original psychedelic experience (e.g. listening to the dosing session playlist), suggesting a memory-based mechanism. Alternative explanations, such as memory reconsolidation (Lee, 2009; Sinclair & Barense, 2019), state-dependent recall (Dunsmoor et al., 2015; Eich, 1980; Girardeau et al., 2017; Radulovic et al., 2017), or changes in default mode network activity (Carhart-Harris & Friston, 2010, 2019; Ortiz Bernal et al., 2022), may better account for the observed phenomena. Ultimately, rigorous neuroimaging and EEG studies are needed to directly investigate the neural correlates of reactivations and gain a more comprehensive understanding of this phenomenon.

Strengths and Limitations

A key strength of this study is the inclusion of a Spanish-speaking sample, adding valuable diversity to the existing literature, which has predominantly focused on English-speaking populations. This broader representation helps ensure that the findings are more generalizable across different cultural contexts. The study provides important preliminary data on the prevalence, predictors, and emotional valence of reactivations associated with 5-MeO-DMT use, which can help inform prospective longitudinal clinical studies investigating the therapeutic applications of 5-MeO-DMT in rigorous placebo-controlled trials with diverse populations.

Despite these strengths, several limitations of this study merit careful consideration. First, the small sample size is a significant limitation. Although 379 respondents consented to participate in the 5-MeO-DMT survey section of the larger study, only 90 began and completed it. We had initially expected at least 300 respondents. Second, the cross-sectional nature of this survey prevents us from inferring any causal relationships between the variables analyzed.

Prospective longitudinal designs are needed to further examine if these associations withstand more rigorous research designs. Third, retrospective survey studies are generally limited by recall bias (Coughlin, 1990). Participants may not accurately remember past experiences, which can affect the reliability of the data. Fourth, given the small sample size, we were unable to include some predictors examined in the previous reactivation study (Ortiz Bernal et al., 2022). Specifically, of the 90 respondents, only 62 reported experiencing reactivations, which limited the observations available for the emotional valence logistic regression model (because only those that answered affirmatively to the question "Have you had a reactivation?" were further asked about its associated emotional valence. This reduced statistical power constrained our ability to include additional variables, such as the employment of a series of benefit enhancement strategies, including setting an intention and meditating prior to the 5-MeO-DMT dose, which were previously shown to be significantly associated with reactivations (Lancelotta & Davis, 2020; Ortiz Bernal et al., 2022).

Additionally, the present study's findings, which primarily show positive effects of reactivation events, are further limited by selection bias. Respondents who have experienced negative reactivations may be less inclined to participate in related research due to potential discomfort, distress, or dissatisfaction with their experiences. Consequently, their perspectives may not be adequately represented in this study. Alternatively, those who have had negative experiences might be motivated to share their stories as a form of warning or advocacy, but this study did not capture such participation. Suggesting a bias toward more positive reports. Future research, including ongoing and forthcoming clinical trials with various 5-MeO-DMT formulations in commercial development, is necessary to provide further insights and validation of these findings. Nevertheless, this study sheds light on the prevalence rates, predictors and

emotional valence of the reactivation phenomenon among a sample of Spanish-speaking individuals. It expands and complements the limited scientific literature addressing this phenomenon while contributing to greater inclusion and diversity in psychedelic survey studies.

Conclusion

This study provides important insight into the reactivation phenomenon associated with 5-MeO-DMT use among a sample of Spanish-speaking individuals. Our findings reveal that reactivations are prevalent and often perceived as positive or neutral experiences. This suggests that rather than being adverse effects, reactivations may serve therapeutic processes contributing to long-term positive changes, potentially acting as bridges between the acute psychedelic experience and sustained personal growth.

In summary, while both the Spanish-speaking and English-speaking samples exhibited high prevalence rates of reactivations and predominantly positive or neutral emotional valence, notable differences were observed in the predictors of these experiences, such as the absence of gender differences in the Spanish-speaking sample. These findings underscore the importance of considering cultural context in psychedelic research to better understand the nuances of reactivation phenomena and their potential therapeutic implications as well as possible safety concerns.

As research on 5-MeO-DMT progresses towards potential FDA approval, these findings have implications for clinical practice. The presence of negative reactivations in a small percentage of participants highlights the need for careful management and support during the integration process to mitigate these effects, and comprehensive preparation processes to maximize therapeutic outcomes. Future research should focus on identifying specific triggers for negative reactivations, and explore the potential effects of reactivations on clinical symptoms

and well-being long-term. Overall, this study contributes to the growing body of knowledge on 5-MeO-DMT, offering valuable considerations for clinical applications and future research directions. It expands the limited scientific literature on reactivations, while promoting greater inclusion and diversity in psychedelic research.

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Tables

Table 1
Demographic Data and 5-MeO-DMT Use Patterns (n=90)

Characteristic	*M (SD) or %*
Age	38.8 (15.5)
Gender	
Male	67%
Female	33%
Education	
Graduated high school/trade or technical school	17%
Some college – no degree	29%
Associate degree/bachelor's degree	35%
Advanced degree (Master's, Ph.D., M.D.)	19%
Country of Origin	
Andorra	1%
Argentina	7%
Belgium	1%
Bolivia	1%
Chile	2%
Colombia	10%
Costa Rica	2%
Guatemala	1%
Mexico	53%
Spain	4%
United States	9%
Uruguay	1%
Venezuela	7%
Planned Time Ahead	
No plan or a few days	49%
One week/one month/>six months)	51%
Obtained from/Source of 5-MeO-DMT	
Purchased online/ from a friend/stranger	11%
Provided at ceremony	71%
Gifted /Other	18%
5-MeO-DMT Administered by	
I self-administer	18%
Shamanic practitioner/Church leader	62%
Friend/Peer sitter/Treatment center/Other	20%

Table 2

Relationships Between Independent Variables and Occurrence of Reactivation Following use of 5-MeO-DMT Among a Sample of Spanish-speaking Individuals (n=90)

Variables	Bivariate effects			Multivariable effects		
	OR	***95% CI***	***P-value***	***OR***	***95% CI***	***P-value***
Demographic						
Gender (ref =male)	1.08	.41 - 2.80	.872	0.79	.26 -2.43	.686
Preparation						
Planned time ahead (ref=	3.96	1.50 - 10.40	.005*	3.03	1.03 - 8.87	.043*
No plan or few days)						
Acute effects						
Ego Dissolution	1.58	1.04 - 2.39	.032*	1.30	.77 - 2.20	.317
Inventory						
Challenging Experiences	1.69	.98 - 2.90	.058	1.48	.80 - 2.73	.204
Questionnaire						
Psychological Insight	1.50	1.02 - 2.22	.037*	0.90	.55 - 1.49	.707
Questionnaire						
Persisting effects	1.59	1.03 - 2.47	.038*	1.31	.83 - 2.05	.234
PEQ – Meaning						
Psychological changes						
(before/after measure						
Cognitive fusion	2.10	1.33 - 3.33	.002*	1.76	1.021-3.05	.042*

Note: OR= Odd Ratio. CI= confidence interval

Table 3

Relationships Between Independent Variables and Positive Emotional Valence of 5-MeO-DMT Reactivations Among a Sample of Spanish-speaking Individuals (n=90)

Variables	Bivariate effects			Multivariable effects		
	OR	***95% CI***	***P-value***	***OR***	***95% CI***	***P-value***
Preparation						
Planned time ahead (ref=	1.78	.50 - 6.33	.375	1.25	.29 - 5.32	.767
No plan or few days)						
Acute effects						
Ego Dissolution	1.74	.90 - 3.34	.097	1.21	.56 - 2.61	.619
Inventory						
Challenging Experiences	0.52	.29 - .96	.037*	0.43	.20 - .95	.037*
Questionnaire						
Psychological Insight	1.94	1.06 - 3.54	.032*	2.43	1.08 - 5.45	.032*
Questionnaire						
Psychological changes						
(before/after measure)						
Cognitive fusion	1.17	.73 - 1.86	.515	0.97	.49 - 1.94	.941

Note: OR= Odd Ratio. CI= confidence interval

Chapter 4 - Unraveling Narratives: A Cultural and Historical Examination of 5-MeO-DMT Use Among Indigenous Tribes in Ancient South America, the Toad Motif in Mesoamerica, and Modern 5-MeO-DMT uses in North America and Around the World

Abstract

The present paper provides a comprehensive historical and cultural examination of 5-MeO-DMT use among Indigenous tribes in ancient South America and its modern applications. The study explores traditional uses of 5-MeO-DMT-containing plants such as *Anadenanthera peregrina* and *Virola theiodora*. It also delves into a toad motif present in Mesoamerican cultures, particularly as a symbol of duality, renewal, and regeneration.

Despite recent claims of ancestral toad secretion use among the Comcaac (Seri) people of the Sonoran Desert, ethnographic evidence does not support these assertions. The paper highlights the ecological and ethical concerns associated with the rising demand for toad-derived 5-MeO-DMT, emphasizing the need for conservation and culturally sensitive practices.

Additionally, the study addresses the modern therapeutic applications of 5-MeO-DMT, examining its potential benefits for treating various mental health conditions, including depression, anxiety, posttraumatic stress disorder, and substance misuse. The research underscores the importance of rigorous scholarship in understanding the historical and cultural contexts of 5-MeO-DMT use and calls for further investigation into its therapeutic potential and impact on Indigenous practices and ecosystems.

By integrating historical, cultural, and modern perspectives, this paper aims to provide a holistic understanding of 5-MeO-DMT use both in ancient and present times, advocating for responsible and informed use that respects both the natural environment and Indigenous traditions. This multidisciplinary approach highlights the complex interplay between traditional knowledge and contemporary scientific research, paving the way for future studies that could bridge these diverse fields, while fostering more nuanced conversations regarding the present ecological status of the Sonoran Desert toad.

The Present Study

5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) is a short-acting psychedelic that is found in several plant species, including *Anandenanthera peregrina* and *Virola theiodora* (Furst, 1976). The 5-MeO-DMT containing seeds of the *Anadenanthera peregrina (*and *Anadenanthera colubrina)* tree, as well as the bark and resin of the *Virola theiodora* tree are used by various Indigenous groups in South America, including the Taíno, Yanomami, Tukano, Barasana, Yekuana, Waika, among others, in snuff preparations (Guss, 1986; Schultes, 1979; Torres & Repke, 2006). These snuff preparations, known by various names including, *cohoba*, *vilca, yopo, epéna*, depending on the plant source, geographic area and Indigenous group in question, are typically insufflated using foot-long tubes made from bamboo or hollow bird bones, or bifurcated Y-shaped nasal snuff tubes (Safford, 1916; Schultes, 1976; Torres & Repke, 2006).

In North America 5-MeO-DMT also naturally occurs in the defense secretions of an amphibian endemic to the Sonoran Desert bioregion in Southwestern United States and Northwestern Mexico. This unique toad, formerly known by the scientific name *Bufo alvarius* (Weil & Davis, 1994), but currently known by the name *Incilius alvarius*, is the largest amphibian in arid North America, growing upwards to about 20 cm (8 in) (Rorabaugh & Lemos-Espinal, 2016). Its geographic distribution extends throughout southern Arizona, and southwestern New Mexico in the United States of America, and southward into Sonora, as well as some parts of Chihuahua and Sinaloa in Mexico (Frost, 2020).

Although in recent years, claims have been made about ancestral uses of the 5-MeO-DMT-containing toad secretions in ritual settings among the Sonoran Desert tribes, primarily on the part of the Comcaac people (commonly known as “Seri”), the ethnographic record available both from the records of Jesuit priests, as well as from Western ethnobotanists who have

documented the customs and traditions of the Comcaac people does not appear to support said claims (Delgrasso, 2024; Villa, 2023).

The present paper provides a concise historical overview of some of the traditional uses of 5-MeO-DMT containing plants in ancient South America. It also summarizes ethnographic accounts of a prevalent toad motif among Mesoamerica tribes dating back to the 16th century. The paper then examines a contemporary cultural narrative that has emerged in North America over the past 12 years that purports ritualistic uses of 5-MeO-DMT-containing secretions from the *Incilius alvarius'* toad by the Comcaac Indians of the Mexican state of Sonora.

With this as the backdrop, the paper addresses pressing conservation concerns regarding the current ecological status of the toad species, given its escalating exploitation due to rising demand for its psychedelic exudate. The paper concludes by outlining ethical considerations related to both the endemic toad species, and underground practitioners who utilize its secretions in ceremonies worldwide.

Introduction to 5-MeO-DMT: Pharmacology, Phenomenology and Subjective Effects

5-MeO-DMT is a substance with ultra-rapid onset and short duration of psychedelic effects that was first synthesized in 1936 by Japanese chemists Hoshino and Shimodaira (Hoshino & Shimodaira, 1936). Depending on the route of administration, 5-MeO-DMT's onset of acute effects may begin within 30 seconds and be over within 20 minutes (vaporization route), or begin within 3-5 minutes and subside within 45-60 minutes (insufflation, intramuscular [IM] injection route) (Ermakova et al., 2022; Reckweg et al., 2021; Reckweg et al., 2022). 5-MeO-DMT's relatively short duration of action is due in part to rapid deamination by the enzyme Monoamine Oxidase A (MAO-A). A second metabolic pathways involved in the rapid metabolism of 5-MeO-DMT is *O*-demethylation; a process that is catalyzed by cytochrome P450

enzymes, particularly CYP2D6 (Shen et al., 2010). This rapid onset and short duration of acute effects are viewed by some researchers in the psychedelic field as factors that could enhance the accessibility and scalability of psychedelic-assisted therapies (Davis et al., 2019), although other researchers have also expressed skepticism over the shorter compound's capacity to elicit long-lasting therapeutic effect, especially at scale, (Aday et al., 2023).

In contrast to other more extensively studied psychedelics, like psilocybin, the active ingredient in psychoactive mushrooms (e.g. *Psilocybin cubensis*), whose main site of action in the mammal brain is the serotonin receptor subtype 2A (5-HT2A), 5-MeO-DMT is primarily active at a different type of serotonin receptor, namely the 5-HT1A (Dakic et al., 2017; Krebs-Thomson et al., 2006; Szabo et al., 2014). Additionally, 5-MeO-DMT has been found to be active at the orphan receptor, Sigma 1 (sigmar-1), where it is believed to be involved in anti-inflammatory processes that may contribute to its potential therapeutic action (Dakic et al., 2017; Szabo et al., 2014).

The phenomenology of 5-MeO-DMT has been reported as intense and distinct (from other highly visual tryptamines such as its close cousin, *N*,*N dimethyltryptamine* [DMT]), but without visual effects (Ermakova et al., 2022). While the 5-HT2A receptor is highly expressed in the visual cortex, the 5-HT1A receptor expression associated with 5-MeO-DMT is low there, which may account for the lack of a visual component of the 5-MeO-DMT experience compared to psilocybin (Carhart-Harris & Nutt, 2017). However, mechanistic studies with 5-MeO-DMT have yet to be published. Current research is expanding our understanding of 5-MeO-DMT's neurological effects through advanced imaging techniques. At Imperial College London, high-density electroencephalography (EEG) studies on 5-MeO-DMT are in progress (C. Timmerman, personal communication, June 22, 2023), following similar methodologies used in previous

DMT research (Alamia et al., 2020; Timmermann et al., 2019). Concurrently, Dr. Robin Carhart-Harris, renowned for his extensive neuroimaging work with psilocybin and other psychedelics (Carhart-Harris et al., 2012, 2016, 2017; Tagliazucchi et al., 2016), is pioneering the first magnetic resonance imaging (MRI) study of 5-MeO-DMT (R. Carhart-Harris, personal communication, May 12, 2024).

The 5-MeO-DMT subjective experience is often described as transcendent, involving elements of "mystical-type" experiences, ego-dissolution and nondual awareness with an increased range of emotions from awe, love and unity to panic and terror (Delgrasso, 2024; Ermakova et al., 2022). A somatic response ranging from release in muscle tension, shaking or trembling, to primal screaming, dancing (or even running) can also accompany the experience.

Due in part to the growing popularity of toad-derived 5-MeO-DMT use (Delgrasso, 2024; Ermakova et al., 2022; Villa, 2023), in conjunction with preliminary data on its potential therapeutic applications in the treatment of various psychological disorders from naturalistic and observational studies (Davis, Averill, et al., 2020; Davis et al., 2018; Davis et al., 2019; Mangini et al., 2022; Reckweg et al., 2022; Uthaug et al., 2019), various synthesized versions of 5-MeO-DMT are now under investigation in controlled clinical trials (Aday et al., 2023). Current trials registered on clinicaltrials.gov include studies aimed at evaluating the effectiveness of 5-MeO-DMT in the treatment of treatment-resistant depression (Clinical.Trials.gov Identifier: NCT05800860) and post-partum depression (Clinical.Trials.gov Identifier: NCT05804708).

The increasing scientific focus on exploring the potential therapeutic applications of 5-MeO-DMT, coupled with ongoing commercialization efforts by various organizations (such as Usona Institute, GH Research, and Beckley Psytech) to develop it into a regulatory-approved mental health treatment (Aday et al., 2023) underscores the need for a comprehensive

examination of the historical and biocultural context of 5-MeO-DMT use, spanning both ancient and contemporary periods.

In the next section, we describe accounts of ritualistic use of 5-MeO-DMT containing-snuffs documented by various Spanish friars in the 16th century upon contact with diverse Indigenous groups in South America. We also describe examples of a toad motif prevalent among Mesoamerican tribes, including the Aztecs, Mayans, and Mexico's "Mother Culture," the Olmecs. Additionally, accounts from Jesuits priests who encountered the Sonoran Desert tribes in the 17th century and documented traditional customs and practices are reviewed. This is followed by a timeline of recent cultural events that have contributed to the rise in 5-MeO-DMT popularity over the past decade.

Historical Context of 5-MeO-DMT Use

The earliest European accounts of ritual intoxication with plant-based 5-MeO-DMT date to the end of the 15th century. The anthropologist Peter Furst, in his 1976 book titled *Hallucinogens and Culture,* recounts that fray Ramon Pané was commissioned by Christopher Columbus, on his second voyage to the American continent in 1496, to "observe and set down the ceremonies of the Arawakan-speaking Taíno" on the island of Hispaniola (Furst, 1976). Pané described a ritual in which the natives inhaled an intoxicating herb they called *cohoba* that was "so strong that those who take it lose consciousness."

The substance Pané described as *cohoba* was later identified as being derived from *Anadenanthera peregrina* seeds. The main psychoactive compounds in *Anadenanthera peregrina* are actually DMT, 5-hydroxy-*N*,*N*-dimethyltryptamine (5-HO-DMT), aka bufotenine, and 5-MeO-DMT. This identification was made through a combination of ethnobotanical research, linguistic analysis, and archaeological evidence, while the chemical composition of

Anadenanthera peregrina was determined through modern analytical chemistry techniques. In the 1950s and 1960s, researchers like Bo Holmstedt and Jan-Erik Lindgren conducted chemical analyses of *Anadenanthera* samples, identifying the presence of these tryptamines (Holmstedt & Lindgren, 1967).

When describing the ritualistic use of these snuffs, Pané wrote: “This powder they draw up through the nose, and it intoxicates them to such an extent that when they are under its influence they know not what they do” (Safford, 1916).

The Dominican friar Bartolomé de las Casas, as documented by Safford (1916), provides a firsthand account of the *cohoba* ceremony among the Taíno people on the island of Hispaniola (modern day Dominican Republic and Haiti). His description offers valuable insights into the device used for administering the snuff. de las Casas depicts the snuff tray as a refined wooden implement, describing it as "a plate, not flat but slightly concavish or deep." He emphasizes its aesthetic quality, noting that it was "so handsome, smooth, and pretty, that it could not be very much more so, were it made of gold or silver." The friar further characterizes the tray's appearance as "almost black and polished like jet," highlighting its lustrous finish. This detailed observation not only illuminates the physical attributes of the ceremonial equipment but also suggests the cultural significance and craftsmanship invested in these ritual objects by the Taíno people (Ostapkowicz, 2020; Safford, 1916). Of the Y-shaped nasal tube used, de las Casas wrote that the tube:

> …was fashioned the size of a flute and was quite hollow like a flute. From two-thirds of its length onward it divided by means of two hollow canes, just as we open the two middle fingers, leaving out the thumb, with the hand extended. The ends of these two canes inserted into the windows of the nostrils, and the base of the flute, let us say, into the powder on the plate, they would draw in their breath and snuffing up would receive through the nostrils as much of the powder as they wished to take, which, when taken, would go at once to the brain, almost as though they had drunk strong wine; for they would become drunk or almost drunk…(de las Casas, as cited in Safford, 1916)

de las Casas further articulates that use of *cohoba* was customary for coming together to decide difficult matters. He recorded that the chief would begin the ceremony while the others in attendance remained silent. After snuffing the powder up his nostrils, he would utter certain words, to which the rest of the individuals in attendance would respond in unison. The chief then would share his vision, which predicted "…good times or the contrary, or that children were to be born or to die, or that there was to be some dispute with their neighbors, and other things which might come to his imagination."

Torres and Repke (2006) note that the importance of *Anadenanthera* use among the Taíno, and its role in shaping their beliefs and ritual practices, prompts questions regarding its origins and antiquity. They further note that in the Andes, early colonial documents demonstrate that the use of a snuff called *vilca* (from the *Anadenanthera colubrina* tree) was widespread (Torres & Repke, 2006). The south central Andes, spanning Peru, Bolivia, the Atacama Desert of Chile, and northwestern Argentina, holds the most ancient and extensive evidence of *Anadenanthera* preparations. The earliest evidence, dating back 4000 years, originates from northwestern Argentina (Torres & Repke, 2006).

According to Tores and Repke (2006), outside of the Andean region, evidence of *Anadenanthera* use extends across three primary areas: the Orinoco River system, the Amazon basin, and its southern periphery. Documentation of psychoactive plant use in these regions dates back to the late 1600s. Early accounts from missionaries like Joseph Gumilla and the Jesuit Juan Rivero in the 1700s provide some of the earliest descriptions of *Anadenanthera* use. (Torres & Repke, 2006). In the Orinoco basin, including Colombia and Venezuela, use of a potent psychedelic snuff known as *yopo*, which is made with *Anadenanthera peregrina* seeds appears to

be a pervasive and widespread cultural practice carried out for purposes of divination and healing. Among some of the tribes known to have used, or to continue using snuff preparations from *Anadentathera* species are the Guahibo, the Tunebo, the Airico, the Otomac, the Piaroa, and the Yanomano (Schultes, 1979; Torres and Repke, 2006).

In addition to the snuff preparations made from *Anadenanthera peregrina* and *Anadenanthera colubrina* seeds, extensively documented by Torres and Repke (2006) as described previously, snuff preparations derived from the resin of *Virola theiodora* contain significant concentrations of 5-MeO-DMT, ranging from 8 to 11 percent (Agurell et al., 1969; Furst, 1976). These preparations were historically utilized across the Amazon region by tribes such as the Barasana, Tukano, Makuna, Kuripako, among others in Colombia, Venezuela and Brazil for diagnosis and treatment, prophecy and divination, and other religious purposes (Schultes, 1979). The American biologist Richard E. Schultes, who is considered the father of ethnobotany and who visited the Waika (also known as the Yanomani/Yanomano) in 1967, described the method of preparing the snuff as follows:

> There are a number of methods of preparing the snuff, which is called epéna or nyakwana by the many tribes which I include under the generic term Waika. Some scrape the soft inner layer of the bark of the tree, dry the shavings by gentle roasting over a fire, and store them until they are needed for making the snuff. They are then crushed and pulverized, triturated and sifted. The resultant powder is fine, homogenous, chocolate-brown, and highly pungent. (Schultes, 1972, as cited in Furst, 1976, p. 150)

Agurell et al (1969) explain the differences between epéna and nyakwana preparations. Epéna is prepared from the bark of *Virola theiodora* in combination with crushed and powdered leaf material from *Justicia pectoralis,* and mixed with ashes from *Elizabetha princeps.* The nyakwana is prepared only using the resin from the *Virola theiodora* tree.

Unlike the Y-shaped nasal tubes used by the Taíno and other Indigenous groups, the Waika employ long bamboo tubes to administer their prepared snuff in a reciprocal manner. This

involves one person forcefully blowing the finely ground powder through the tube into another participant's nostrils, a practice that continues to be observed among them today (Furst, 1976). See image from page 148 of Furst's book titled *Hallucinogens and Culture* below.

To clarify: *Anadenanthera peregrina* and *Virola theiodora* are two different plant species used in different regions for preparing psychoactive snuffs: *Anadenanthera peregrina* is a tree in the legume family (Fabaceae) used in the Caribbean and parts of South America. *Virola theiodora* is a tree in the nutmeg family (Myristicaceae) used in the northwestern Amazon. Virola species, including *V. theiodora*, generally contain higher levels of 5-MeO-DMT compared to *Anadenanthera peregrina.* The use of Virola was documented much later than *Anadenanthera,* primarily in the 20th century by ethnobotanists like Richard Evans Schultes (Schultes, 1979).

The Toad Motif in Mesoamerica

Besides the accounts of Pané, and de las Casas in the 15th and 16th century, as well as the records of Furst from the 1970's regarding the utilization of various plants containing 5-MeO-DMT to prepare snuffs, Furst and other Spanish friars also documented an extensive toad motif present among various tribes of Mesoamerica.

Toads have long been powerful symbols of duality, renewal, and regeneration in Mesoamerican art and mythology, often embodying themes associated with transcendent experiences. However, historical accounts rarely link toads directly to psychedelic use, highlighting a contrast between ancient symbolism and modern interpretations that connect toad secretions with psychedelic practices, as will be described in a forthcoming section.

The importance of the toad motif in Mesoamerica has been extensively addressed by the anthropologist Peter Furst. The second to last chapter of his 1976 book *Hallucinogens and Culture* titled "The Toad as Earth Mother: A Problem in Symbolism and Psychopharmacology" starts with the following paragraph:

> There is in North and South America a widespread mythic complex that links the toad to the earth as animal manifestation of a dualistic Earth Mother Goddess, at once destroyer and giver of life. Sometimes the toad is the earth, and from her body sprouted the first food plants – maize in Mexico, bitter manioc in Amazonia. She is also benefactress of the first people or culture heroes, teacher of the skills of hunting and the magic arts, and her dismemberment accounts for the origins of agriculture. (Furst, 1979, p.158).

Furst's work touches particularly on the connection between toads and the Aztec earth goddess Tlatecuhtli. Tlatecuhtli, whose name can be translated as "Guardian of the Earth," was a primordial goddess in Aztec cosmology (Furst, 1976). She was often depicted as a monstrous, toad-like figure with a gaping mouth, representing the Earth that devours all life in death, and gives birth to new life. Furst explored how toads were symbolically associated with earth, fertility, and rebirth across various Mesoamerican cultures, noting similarities between

depictions of Tlatecuhtli and certain toad imagery, such as the wide open and squatting posture often seen in representations of both (Furst, 1976).

In Aztec creation myths, Tlatecuhtli was a fearsome monster of the primordial waters. According to one version of the myth, the gods Quetzalcoatl and Tezcatlipoca transformed themselves into serpents and tore her in half. From her upper body, they created the earth, and from her lower body, the sky. Her hair became trees, flowers, and grass; her skin became the surface of the earth; her eyes became caves, wells, and springs, her mouth became rivers and large caves, and her nose became valleys and mountains (Maestri, 2023).

Furst (1972) also notes that this myth of the Toad Mother and Culture (Twin) Heroes is echoed in older stories from South America, extending all the way into the Andes. This older myth that Furst documents goes like this:

> Before the birth of the divine hero twins, their natural mother is killed by the Jaguar People. However, the unborn twins are saved by Toad Grandmother, who is Mistress of the Earth, Owner of Fire, as well as Mother of the Jaguars, and who herself has feline characteristics and can change back and forth between jaguar and amphibian forms. The manner in which she preserves the unborn twins differs somewhat from area to area – often it is the eggs with the children inside, or else the pregnant uterus, which she places close to her magical fire. Eventually the twins emerge and she rears them, teaching them to hunt, cure, etc. They, in turn, have vowed to avenge the death of their natural mother, and as the foster mother is also Mother of the Jaguars, they kill her and dismember and incinerate her body in a clearing in the forest. From the dismembered toad sprout first of all cassava, or bitter manioc, and other useful plants. Manioc, which in its natural state is poisonous, is identified with the milky secretion flowing from the venomous glands in the toad's skin. Apart from these details the parallel between the dismemberment of Toad Grandmother by the divine twins and that of Tlatecuhtli by Tezcatlipoca and Quetzalcoatl is unmistakable”(Furst, 1972).

Furst further argues that this toad and divine twins myth transcends linguistic, cultural and geographical boundaries, and that similar traditions are found among a wide range of Indigenous peoples, including the Caribs, Arawakans, Tupians, Warao, Waika and other. He notes that perhaps one of the most interesting versions of the Earth Mother as a monstruous, dualistic toad

is found among the Tacana from Bolivia where she is described as being the bringer of cultivated plants, similar to the accounts found across South America. Interestingly, in the Tacana version of the myth, it is the dualistic toad who also teaches people how to make the first hallucinogenic snuff (Furst, 1972).

Cultural and Symbolic Meaning in Mesoamerican Art

The toad motif in Mesoamerican art holds significant cultural and symbolic meaning across various civilizations, including the Aztecs, as well as the Mayans and Olmecs (Miller, 2006). Toads were often depicted in artwork and iconography, representing different concepts such as fertility, transformation, duality, and connection to the spirit world. Toad sculptures span a wide range of sizes, from small to colossal (3–130 cm; 0.39 – 51.18 inches) (Miller, 2006). These sculptures have been discovered at Izapa in Chiapas, Mexico, dating back to the late Preclassic period, approximately 300 BC to AD 250 (Guernsey, 2006). Toads were prominently featured on structures known as toad altars and also depicted in relief carvings on stelae. The relief sculptures of toads at Izapa are notably large, with dimensions of approximately 120 cm in length and 80 cm in width. According to Julia Guernsey (2006), Stela 6 clearly represents *Bufo marinus*, the giant toad or cane toad of the Bufonidae family, identifiable by the distinct parotid glands on its back, depicted as expelling an object from its mouth.

Stela 6 at Izapa showing the parotid glands of *Bufo marinus*, depicted as expelling an object from its mouth. Image from http://www.famsi.org/research/pohl/sites/izapa.html

In Aztec and Maya cultures, toads were associated with rain deities and agricultural fertility due to their amphibious nature, which linked them symbolically to water and renewal. In Aztec culture, toads were associated with the rain god *Tlaloc*, who was revered for his role in bringing rain and fertility to the crops, crucial for agricultural prosperity. Toads symbolized water and fertility due to their connection to aquatic environments and their ability to survive both on land and in water (Smith, 2011).

Among the Maya, toads were also associated with water and fertility but were linked to the rain god *Chaac (Delgrasso, 2024)*. In Maya mythology, Chaac was depicted as a deity with toad-like features or as attended by toad companions. For the Mayans, as with the Aztecs, toads were seen as embodying the spirit of water and were thus considered powerful symbols in rituals aimed at ensuring rainfall and agricultural success. Their presence in Mayan art underscores their role in rainmaking ceremonies and agricultural fertility rites (Miller, 1993).

The Olmecs, considered the earliest major civilization in Mesoamerica, also incorporated toads into their art. Though less extensively documented compared to later civilizations, Olmec art shows representations of toads as part of their cosmological and mythological beliefs. As with

the Mayans and the Aztecs, toads in Olmec art are interpreted as symbolic beings associated with earth fertility and spiritual transformation (given their striking metamorphosis process from tadpole to toad), echoing broader Mesoamerican beliefs in the transformative power of amphibians.

These motifs reflect the deep cultural and spiritual significance of toads in Mesoamerican societies. With the Olmecs, there is another intriguing aspect documented in the anthropological record, which is that at various Olmec sites *Bufo marinus* bones have been found in great numbers and often in ritual contexts (Cyphers et al., 2005; Davis, 2023; Kennedy, 1982). Of note, although *Bufo marinus* does secrete bufotenine through their parotid glands, bufotenine is now known to not have psychedelic properties the way 5-MeO-DMT present in the *Bufo (Incilius) alvarius* toad does (Weil & Davis, 1994).

The above description of toad iconography in Mesoamerican art is being offered as background information to evaluate it as proof (or lack thereof) that 5-MeO-DMT was used in ancient times.

Modern Uses of 5-MeO-DMT

In a subsequent section, we will examine how certain interpretations of Mesoamerican art have been used to assert, with questionable certainty, the ritualistic use of *Incilius alvarius* toad secretions among the Aztecs, Mayans, and Sonoran Desert tribes (Rettig Hinojosa, 2016). These assertions, often extrapolated from interpretations of Mesoamerican art and mythology, suggest a continuity of ritual practices involving psychoactive substances. However, the reliability and accuracy of these interpretations remain contentious and require careful scrutiny. Before addressing these assertions, it is important to first provide context by outlining the emergence and development of 5-MeO-DMT use in contemporary society.

An interesting historical fact to state at the outset of this modern timeline is that while psychedelics like psilocybin, and Lysergic acid diethylamide (LSD), were classified as Schedule 1 substances under the Controlled Substances Act of 1970, 5-MeO-DMT remained unscheduled until 2011. Ralph Metzner was a prominent psychologist and researcher who played a key role in the 1960s psychedelic movement, notably collaborating with Timothy Leary and Richard Alpert (later known as Ram Dass) at the Harvard Psilocybin Project (Leary et al., 1963). In his 2013 book *The Toad and the Jaguar*, Metzner detailed his underground explorations with 5-MeO-DMT and the concerted effort by the underground community of the 1960s to maintain a low profile around 5-MeO-DMT use to prevent scheduling. Their efforts proved successful, as evidenced by 5-MeO-DMT remaining unscheduled until 2011 (Metzner, 2013).

How did 5-MeO-DMT evolve from such an obscure substance, avoiding federal scheduling well into the 2000s to its current popularity? This shift is evident in numerous articles across diverse media outlets, even unexpected ones like *Forbes* magazine. Titles such as *"5-MeO-DMT: The 20-Minute Psychoactive Toad Experience That's Transforming Lives," "GH Research Goes Public To Turn 5-MeO-DMT Into Medicine For Treatment-Resistant Depression," and "Could 5-MeO-DMT Allow For More Affordable Psychedelic-Assisted Therapy? Beckley Psytech Thinks So,"* reflect the growing economic interest in 5-MeO-DMT. This substance is increasingly viewed as an economic commodity, and potential mental health panacea, underscored by the flurry of patent applications aimed at developing it for various mental health conditions.

According to the online database, *Porta Sophia*, which is dedicated to documenting existing knowledge in the psychedelic field **(e.g. psychedelic prior art)** that might be relevant to a patent's claim of **novelty (U.S. law patentability requirement 35 U.S.C. §§ 100-103)**, as of

April 2022, there were 76 5-MeO-DMT patent applications. Of these, 57 were evaluated as "Tier 1." In the context of Porta Sophia's patent classification system, Tier 1 typically refers to patent applications that have overly broad claims. These claims might cover a wide range of potential applications or methods, **often referencing existing technologies and knowledge already in the public domain.** Tier 1 patents are considered problematic because they could **sequester existing practices and** pose challenges to future accessibility of psychedelic treatments (Li et al., 2023; Ortiz et al., 2022)

5-MeO-DMT: From Obscure Underground Use to Massive Widespread Global Popularity

Over the past 12 years, awareness of toad-derived 5-MeO-DMT has surged as a result of being featured in various episodes of the popular show *VICE TV* (Vice, 2015) and numerous documentaries that have propagated a cultural narrative of purported ancestral use of the toad secretions by the Seri people of Punta Chueca, Sonora (de Greef, 2022).

But how did awareness about the presence of 5-MeO-DMT in the toad's skin glands spread in the modern world in the first place? Awareness of the extra enzyme required to convert bufotenine into 5-MeO-DMT in "virulent concentrations" (Villa, 2023) in the skin glands of the Sonoran Desert toad is credited to the work of Vittorio Erspamer.

Erspamer, an Italian pharmacologist renowned for his pioneering work, notably discovered serotonin in the rabbit's gastric mucosa in 1935, initially naming it 'enteramine' before it was later renamed serotonin (Whitaker-Azmitia, 1999). His research extended to studying the skin and secretions of toads, particularly those belonging to the *Bufo* genus (Erspamer et al., 1965). Among his numerous discoveries, Erspamer identified and characterized a group of bioactive compounds known as bufotoxins present in toad skins. Notably, he found significant quantities of 5-MeO-DMT specifically in the skin of the *Bufo* (now *Incilius*) alvarius

toad. This discovery was attributed to a unique enzyme in the alvarius toad that converts bufotenine, found in all *Bufo* toads, into 5-MeO-DMT (Erspamer et al., 1965, 1967). Erspamer's groundbreaking findings on the presence of 5-MeO-DMT in toad skin were initially published in academic journals in 1965 and subsequently in 1967, making this knowledge accessible to the scientific community but not widely known to the general public.

More widespread awareness about the presence of 5-MeO-DMT in the toad's skin secretions is owed to Ken Nelson, a researcher from the University of North Texas and conservation advocate who encountered the work of Erspamer. Fascinated with Erspamer's findings, and inspired by an article he had read in *Omni* magazine related to toad remains in an archeological site (Villa, 2023), Nelson began independent research that led him to Arizona in search of the toad. In Gila, Arizona Nelson found the toad and smoked its dried secretions. He is ostensibly the first person in the modern age to do so (Romero, 2022; Villa, 2023). In 1984, Nelson, under the pseudonym "Albert Most," authored and published a pamphlet about the psychedelic properties of the Sonoran Desert toad. Titled "*Bufo alvarius*: the psychedelic toad of the Sonoran Desert," the illustrated pamphlet contained detailed information on how to express the toad's skin glands to harvest 5-MeO-DMT, and instructions on how to smoke it (Most, 1984).

In the mid-1990s, the anthropologist Wade Davis and integrative medicine doctor Andrew Weil published two articles related to the psychoactive properties of the toad (Davis & Weil, 1992; Weil & Davis, 1994), after being introduced to the practice of smoking toad-derived 5-MeO-DMT by a man referred to as "White Dog" (Davis, 2019). After the publication of these papers, a small group of people in Arizona began experimenting, but use of the toad secretions remained a rare occurrence among the few psychonauts that knew of it throughout the 1990s and

early 2000's. Popularity of the 5-MeO-DMT-containing toad secretions did not spread worldwide until 2012 when an false narrative of ancestral use by the Seri Indigenous people of Sonora was introduced into the contemporary cultural milieu by members of a Hermosillo-based non-profit organization called Fundación OTA.C. (de Greef, 2022).

The Seri (Comcaac) People of Sonora

The Seri people, who call themselves Comcaac (meaning "the people" in their language), are an Indigenous group located in the state of Sonora, northwestern Mexico. Their traditional territory spans the coastal desert regions along the Gulf of California and includes Tiburón Island, the largest island in Mexico (Narchi et al., 2015).

Historically, the Comcaac were nomadic hunter-gatherers and skilled fishermen, adapting to the harsh desert and marine environment of their homeland (Felger & Moser, 1985). Today, while many Comcaac continue to rely on fishing and the gathering of desert plants, they have also incorporated modern economic activities, including ecotourism and the production of traditional (and modern) crafts.

The Comcaac have maintained much of their traditional culture and language. The term "Seri" is an exonym, likely derived from the Opata language, while "Comcaac" is their autoethnonym, reflecting their self-identification. This distinction between external and internal naming conventions highlights the importance of recognizing Indigenous self-designation in cultural and anthropological discussions (Marlett, 2018).

With regard to traditional crafts, the Seri are known for their intricate basketry, ironwood carvings, and distinctive musical traditions (Felger & Moser, 1985). Of note though, as David Yetman (Yetman, 1988) and others have documented (Johnston, 1968; Ryerson, 1976), while basket making is indeed an ancient traditional activity, practiced mostly by women, ironwood

carving is a relatively newer craft developed in the 1960s as a tourist fueled economic activity. Felger & Moser (1985) explain that this ironwood carving practice is neither “traditional nor introduced,” but rather, it developed as a result of drastic acculturation, deceases in sea turtles and certain fish species, and increases in tourist interest (Felger & Moser, 1985).

The Comcaac Indians began ironwood carving at the suggestion of a tourist in 1963. Helen Derwin, a resident of Arizona, who was a frequent visitor to Comcaac territory encouraged Jose Astorga, who is generally recognized as the father of ironwood carving (Johnston, 1968), to begin to carve ironwood. By 1968 University of Arizona students began making monthly trips to Comcaac territory to purchase ironwood carvings for resale back in the United States, increasing demand rapidly. David Yetman, in his book *Where the Desert Meets the Sea*, recounts his many trips to Comcaac territory to purchase baskets and ironwood carvings to take back to Arizona to sell and distribute around the world (Yetman, 1988). This aspect of a practice deemed traditional but actually being a relatively modern development in response to cultural forces will be further elaborated in a forthcoming section in relation to the emergence of the toad-smoking practice among contemporary Comcaac Indians in Puenta Chueca, Sonora. But first, in the next section, a brief overview of Comcaac’s traditional practices and their relationship (or lack thereof) with toads is presented.

Analysis of Ethnographic Studies

The ethnobotanical research by Felger and Moser in the 1980s suggested that amphibians were largely inconsequential to Comcaac culture, with the generic term "*otac*" used to describe all such creatures (de Greef, 2022; Felger & Moser, 1985).

Despite this, recent claims have emerged since 2012 asserting that the Seri people “ancestrally” used secretions from the *Incilius alvarius* toad for psychedelic purposes, a practice

allegedly forgotten due to colonization and now being "reintroduced" by outsiders (de Greef, 2022). In Felger and Moser's comprehensive book about the ethnobotany of the Seri Indians, there is only one small paragraph devoted to amphibians. It reads:

> Over most of the Seri region the amphibian fauna is represented by only a few species of desert toads in the genera Bufo and Scaphiopus (spadefoot toad). They occur at scattered localities on the mainland, and Bufo punctatus and Scaphiopus couchi breed at Sauzal water hole on Tiburón Island. They were inconsequential in Seri culture and the several species were not differentiated by name. Toads and frogs were called *otác ziix ano quiij* = a thing that sits on water.

And yet, over the past 10 years or so, the word *otac* has become synonymous with an alleged "ancient sacred medicine ceremony," as depicted in Leonardo Bondani's documentary *OTAC & The Sacred Ancient Medicine Ceremony* (Bondani, 2019), and the first episode of the online series *Shamans of the Global Village* (Heckman, 2015). Both of these documentaries feature prominently a controversial figure, Octavio Rettig Hinojosa, who claims to have reintroduced this practice of smoking toad secretions to the Comcaac people, as articulated in his book *The Toad of Dawn: 5-MeO-DMT and the Rising Cosmic Consciousness* (Rettig Hinojosa, 2016) and further verified and fact-checked by a long-feature article in *The New Yorker* magazine titled "The Pied Piper of Psychedelic Toads" by South African journalist Kimon de Greef (de Greef, 2022).

Although there is ample historical evidence of psychedelic use among Mesoamerican cultures, including the use of psilocybin mushrooms by the Aztecs, which was documented by the Franciscan friar Bernardino de Sahagun in the Florentine Codex, (Furst, 1976), there appears to be no reliable historical documentation of such practices with toad secretions among the Seri or any Mesoamerican tribes. The Jesuit priests that came into contact with the Seri in the 17th and 18th centuries, including most notably, Padre Eusebio Kino, mainly documented his efforts to convert the Seri to Christianity, as well as general observations about Seri life, customs, and

environment. His records, which are valuable for understanding certain aspects of Seri culture at that time, do not contain any mention of the use of toad secretions or similar psychoactive substances (Bolton, 1919). The recent claims, primarily popularized by Rettig Hinojosa (2016) lack substantial historical or anthropological support and should be viewed critically. This situation raises concerns about potential cultural appropriation and the misrepresentation of Indigenous practices, highlighting the need for careful examination of such claims against rigorous scholarly research (Horák et al., 2019).

The work of contemporary Mexican scholar Alí Cortina Bello comprehensively describes the situation that has been unfolding around the purported ancestral use of toad secretions by the Seri people. Cortina Bello conducted an ethnographic study and documented the "otac" phenomenon expansion from Hermosillo, the capital of the state of Sonora, to Mexico City. In the next paragraph, Cortina Bello is cited verbatim, only translating from Spanish to English to illustrate how this ancestral use narrative expanded over the past 10 and how it is currently playing out (Cortina Bello, 2021).

> In the first two decades of the 21st century, we have glimpsed how consumption of psychoactives such as peyote, mushrooms, and recently, Bufo alvarius toad, among many others, is being socially tolerated and reinterpreted by a growing part of the population, because according to the field work carried out in Mexico City, instead of being considered poisons or "drugs," it is said they are "medicines" capable of curing all kinds of psychoemotional pathologies such as addictions; that instead of being a "diabolical" affair, they are a "spiritual illumination that expands consciousness"; and that instead of being a delay to the development of the country, now they are a source of pride and a way of life as part of the Indigenous ancestral heritage.

Cortina Bello analyzes the case of a ceremonial center called "Centro Ceremonial Kalmekayotl" (CCK) that offers weekly ceremonies of various "*ancestral medicines,*" such as peyote, mushrooms, and toad (otac). He explains how both the use of peyote and otac in the ceremonies held at CCK throughout the study period were possible through having obtained a permit from a

mara'kate (Huichol healer) from the Wixárika culture in the case of the peyote ceremonies, and a permit from members of the Comcaac tribe in the case of the toad sessions.

And so here we see the first instance in which a model of obtaining a "permit" from a Comcaac tribe member is supposed to legitimize and qualify the individual to administer toad-derived 5-MeO-DMT as a therapeutic option for various mental health ailments or for spiritual exploration purposes. This narrative of having obtained permission from a Comcaac elder to conduct ceremonies with the toad secretions was first articulated by Rettig Hinojosa (2016). This is a narrative that has been echoed in other parts of the world and by different individuals, first in Mexico City, as described by Cortina Bello in the case of the ceremonial center, and since then in many other settings as will be described below.

Cortina Bello collected the testimony of one of the ceremony organizers and otac facilitators at CCK:

> The otac is a fairly recent offering, it was just barely this year that I started to work with it. It was mainly when I tried it with Dr. Octavio Rettig… we have had other medicines, ayahuasca, yagé, kambó, but the vision that makes that medicine (toad) special, along with peyote, is that they are the medicines of México.

In his testimony, the CCK facilitator further explains that to be able to offer sessions:

> … I had to go with the Seris, along with the doctor (Rettig Hinojosa) so he could introduce me to the whole process, from going to look for the Bufo alvarius out in the desert, learn how the molecule was extracted, what glands are used, go talk with the Seri grandfather Pancho, participate in ceremonies, support the community so that I could get something like a permit within that lineage of Grandfather Don Pancho, and currently we are already directing (otac) ceremonies at CCK.

Cortina Bello further explains that after a group of visitors to CCK who were there for an otac ceremony arrived onsite for the weekend, the facilitator explained what the otac medicine consists of, speaking of its "ancestrality" and emphasizing that he has been given permission through Don Pancho's lineage from the Comcaac tribe, and that it should be seen as an

"ancestral and spiritual medicine" with great healing power. Here we see the beginning of the false narrative perpetuation of the toad as an "ancestral medicine" that gets legitimated through a Comcaac elder's lineage. The problem is: There is no such lineage. The elder in question was actually introduced to 5-MeO-DMT by Rettig Hinojosa and Fundación OTA.C. in 2011 (de Greef, 2022; Villa, 2023), as documented by Rettig Hinojosa himself (Medrano, 2024; Rettig Hinojosa, 2016) and corroborated by de Greef (2022). Cortina Bello concludes the first chapter of his thesis with the following words:

> Obtaining said symbolic permission, ought to be highlighted as one of the most important elements in the logic of the global use of these resources because it creates an extension of the ethnic aura towards the directors of these ceremonies, who are responsible for interpreting and enacting the practices associated to these psychoactive resources.

In this way, Cortina Bello documents how facilitators in México City have endowed themselves with an aura of legitimacy by establishing relationships with members of the Comcaac (Seri) Indigenous tribe of Sonora, and how obtaining such a symbolic permission from a tribe member is crucial to be able to give toad medicine to other people.

This pattern of association to a Comcaac elder as a means to self-legitimize has expanded outside of Mexico City, with numerous facilitators traveling extensively around the world claiming access to a Seri permit to carry out their work in this copycat way. A good example is the case of an American medical doctor who had previously worked at a prestigious medical institution, but has in recent years dedicated himself fully to working with toad secretions, traveling around the world, doing ceremonies for people from all walks of life (Bustani, L., personal communication, May 2024).

At one point during the research for the present paper, this American medical doctor was listed on the website of a retreat company that stated the following: "The elders of the (Seri) tribe are coming together to share their sacred, ancient, ancestral wisdom and ceremonies with us such

as a desert sweat lodge, energy healings, Bufo Alvarius ceremonies as well as their unique cosmology." The above quote further reflects what Cortina Bello documented, specifically that:

> In the case of Comcaac (Seri) it is very clear that some facilitators and other intermediaries have taken advantage of presenting said psychoactive (toad) as an "ancestral medicine" of this culture, despite this being a recent practice whose history isn't clear, and that only a few years ago began to be used in México. On the trip to the Comcaac community of Punta Chueca, Sonora, carried out in March 2017, as part of a support trip organized by Fundación Despierta and Ayuda A.C. – the legal extension of the Kalmekayotl Ceremonial Center– we were able to corroborate how is it not a tradition of an ethnic community. It's just a family of Hacco cama (Traditional specialist who heals with songs and dances) who have recently adopted and recognized the toad as a spiritual medicine, and for the rest of the community it is a completely unknown. (Cortina, 2021).

The Comcaac family in question, the Barnett clan (Kilham, 2023) has indeed capitalized on this narrative, and claimed it as their own in different ways, as evidenced by the huge rise in ecotourism to their territory by people who travel there from all over the world in search of a "legitimate" traditional medicine experience. A Sonora tourism website lists several Seri individuals who offer "otac" as part of the traditional attractions to the area (see https://www.visitsonora.mx/blog/item_en.php?id=40).

On this point, we see a somewhat analogous situation to the ironwood carving craft discussed above, which though not an ancient traditional practice, was embraced initially by one man, Jose Astorga, and his daughter, Aurora Astorga in the 1960's (Johnston, 1968), and from there, the practice expanded to the rest of the Seri Indians as an important economic activity (Ryerson, 1976).

The utilization of toad secretions in ritualistic settings began with one Comcaac elder, Don Pancho Barnett, whom Rettig Hinojosa befriended in 2012. Over the past 13 years, this practice has evolved into a new economic activity among many Comcaac Indians. It includes offering 'otac ceremonies' within Comcaac territory to an increasing number of tourists each year. Additionally, there is a growing demand for these secretions, which are now sold by the

kilogram. Reports indicate that the value can reach up to $50,000 per kilogram, with distribution extending to distant locations such as New York, Los Angeles, and Europe (Kilham, 2023b)."

Impact and Ethical Considerations

As has been described in the preceding sections, the interpretations of Mesoamerican art and mythology regarding toads have been subject to confabulation, particularly concerning claims of ancient ritualistic use of toad secretions among the Seri people (Delgrasso, 2024; Villa, 2023). This paper has endeavored to underscore the importance of critically examining historical narratives and archaeological findings to avoid perpetuating misconceptions about purported ancient ritual practices. By contextualizing the cultural significance of toads within broader Mesoamerican cosmologies, it has been our aim to foster a more nuanced understanding of legitimate Indigenous traditions and their contemporary implications in psychedelic discourse.

Contemporary scholars have begun to articulate the effects and impact of the spread of this alleged narrative that purports the use of *Incilius alvarius* toad secretions as an ancient practice, and the rising demand that results from this cultural narrative. Villa (2023) explains that although the toads are not killed by milking, intensification of this practice does cause stress-induced interruptions in the life cycle of the toad species. Additionally, he has expressed his concern for the extraction and relocation of large specimens that is taking place, which he argues can lead to what is known as “localized extinction.” Indeed, the *Incilius alvarius* toad, once found in generous amounts in California, has not been seen since 1955 and is believed to now be extirpated there (Thomson et al., 2016). In New Mexico it is currently considered a threatened species, and the increasing demand in Sonora and Arizona is certainly impacting the toad’s population trends and dynamics (Villa, 2023).

In the summer of 2023 National Geographic published an article titled “This toad can get you high – really, really high. Poachers have taken notice” (Peterson, 2023). The article underscores how this species is characteristic of the region, along with the Saguaro cactus and the Desert Tortoise, and that if it were to disappear it would represent a significant biocultural impoverishment to the region, and the world. The concern of this vanishing possibility comes as a result of the increasing poaching, for recreation, therapeutics, and profit purposes, the toads have been subjected to, both by locals and visiting foreigners seeking to get high or make a living at the toad’s expense. The article further notes that there are a growing number of expensive retreats where toad-derived 5-MeO-DMT ceremonies are offered, and how celebrities’ positive testimonials of their experiences with the toad are inspiring even more individuals to seek the psychedelic experience engendered by smoking the secretions. Additionally, there are various toad churches being created that state “we’re a church, and this is our sacrament” (smoking toad secretions), and claiming that “we would never go synthetic” (Romero, 2022).

Taken together, all these cultural forces, on top of the global amphibian crisis the 21st century is experiencing, which threatens the extinction of up to 40 percent of amphibians worldwide in the next 50-100 years (González-Del-Pliego et al., 2019; Scheele et al., 2019), represent a formidable force against the continued viability of *Incilius alvarius* in its endemic habitat, the Sonoran Desert (Peterson, 2023).

Currently, the toad is considered to be a species of “least concern” according to the International Union for the Conservation of Nature (IUCN) Red List. However, this classification may no longer be reflective of the actual toad’s ecological status, given the cultural forces that have been encroaching on the species over the past decade. Since 2020 the author, along with herpetologist Georgina Santos Barrera, who contributed to the IUCN’s assessment in

2004 (https://www.iucnredlist.org/species/54567/11152901), have been conducting a toad population study in Sonora. Preliminary findings indicate that despite adequate rainfall and the presence of other toad species, the *Incilius alvarius* toad is notably absent from many of the localities monitored, suggesting a decline in those populations. The study aims to advocate for a re-evaluation of the toad's conservation status on the IUCN Red List, proposing a more protective classification to try to mitigate further population declines in Sonora.

Conclusion

The examination of 5-MeO-DMT use across time and cultures reveals a complex tapestry of human interaction. From the ancient snuffs of South American and Caribbean to the modern global interest in toad secretions, 5-MeO-DMT has played a significant role in spiritual, cultural, and now scientific domains. Our exploration has uncovered the deep roots of 5-MeO-DMT-containing snuffs use in Indigenous South America with plants like *Anadenanthera peregrina* and *Virola theiodora*. Simultaneously, we've seen how the toad motif in Mesoamerican cultures, while rich in symbolism related to fertility and rain, has been misinterpreted and conflated with modern practices. The case of the Seri people serves as a cautionary tale, illustrating how easily narratives of "ancient use" can be constructed and propagated without historical foundation, underscoring the need for rigorous scholarship in ethnobotanical and anthropological studies.

This paper's primary objective has been to critically examine the historical and cultural context of 5-MeO-DMT use, with particular focus on claims regarding Seri traditions. In doing so, we aim not to undermine the economic opportunities of the Seri people, but rather to emphasize the importance of toad conservation and promote a more ethically grounded approach to 5-MeO-DMT use. By scrutinizing narratives of Indigenous practices, we seek to discourage

the proliferation of unsubstantiated new-age interpretations and instead foster a more responsible, culturally sensitive, and ecologically sound discourse.

The recent surge of interest in 5-MeO-DMT from Sonoran Desert toad secretions, brings to light critical ethical and conservation concerns. As modern society grapples with the potential therapeutic applications of 5-MeO-DMT, we must remain mindful of the impact on ecological systems and species that have been on earth for millions of years. The contrast between traditional use of plant-based sources and the current focus on animal-derived 5-MeO-DMT highlights the shifting dynamics of human-nature interactions in the pursuit of altered states of consciousness. The present examination reveals the intricate interplay between culture, science, and ethics in the realm of psychedelic research and therapies. It underscores the importance of approaching such topics with cultural sensitivity and scientific rigor.

Much discernment and congruence is needed at this time and moving forward. Biologist Robert Villa believes that "*public outreach illustrating the dissonance between extractive capitalism and bio-cultural reality will begin to alleviate a growing misunderstanding and demand for this species and its world* (Villa, 2023). It is our hope that the information presented in this manuscript may contribute towards generating the dissonance Villa speaks of, so that ethical considerations regarding the implications of using toad secretions may begin to be examined more carefully.

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Chapter 5 - Conclusion

Psychedelics in general, and 5-MeO-DMT specifically, have gained significant interest as novel and effective treatments for a wide range of mental health disorders in recent years. Some of the neurobiological mechanisms underlying psychedelic's salutatory effects on mental health have been elucidated to date. There is ample evidence that, at the molecular level, psychedelics work by interacting with specific serotonin receptors, namely the 5-HT2A receptor (Dos Santos et al., 2021; Glennon et al., 1984; Madsen et al., 2019; Vollenweider et al., 1998). Although 5-MeO-DMT also interacts with the 5-HT2A receptor, it is unique among psychedelics not only for its powerful capacity to reliably induce profound ego-dissolution experiences, but also for its higher affinity for a different type of serotonin receptor, namely the 5-HT1A, which may account for its distinct phenomenology (Ermakova et al., 2022).

Psychedelics' psychological mechanisms of therapeutic action are less well developed, and it is only in the last few years that hypotheses have begun to be proposed to try to explain psychedelics' therapeutic effects across diagnoses. Since the early days of psychedelic research at Harvard University in the 1960s (Pahnke, 1969), and the early 2000s at Johns Hopkins University, the elicitation of a so-called "mystical experience" has been reliably found to be a robust predictor of psychedelics' therapeutic effects short and long-term (Griffiths et al., 2008; Griffiths et al., 2016; Griffiths et al., 2018; Griffiths et al., 2011; Griffiths et al., 2006). However, the mystical experience framework is increasingly being challenged and some researchers warn against its pervasive indiscriminate use to explain psychedelics' positive effects on mental health (Sanders & Zijlmans, 2021).

New constructs have been proposed to move away from the mysticism framework and onto more secular explanations. Ego-dissolution is one construct that while still capturing

psychedelics' transcendent qualities, is devoid of spiritual or religious overtones and encompasses psychedelic's acute effects well (Nour et al., 2016). Emotional breakthrough experiences is another construct that has been proposed to account for psychedelic's capacity to induce long-term increases in well-being (Roseman et al., 2019). Emotional breakthrough experiences are profound experiences that often involve confronting and processing difficult emotions or memories, which suggests (and some findings validate) that even challenging experiences, when properly supported and integrated, can lead to personal growth and positive change. However, by the same token, it is important to acknowledge that if persistent and not properly cared for, challenging experiences can also lead to adverse consequences causing significant distress, and so responsive management and proactive risk mitigation are of critical value in optimizing psychedelics' therapeutic effects (Greń et al., 2023).

The construct of psychological insight, as proposed by Davis and colleagues (Davis, Barrett, So, et al., 2021) is another important construct that has been put forth to account for psychedelics' capacity to elicit transformative psychological effects. Psychological insight refers to the process of gaining meaningful realizations about oneself, others, or the world that positively influences behavioral change, mood and cognitions. Psychological insight can often be a catalyst for psychological flexibility (Watts & Luoma, 2020), which has been found to be associated with reductions in clinical symptoms of anxiety, depression, racial trauma, PTSD, and substance misuse (Davis, Averill, et al., 2020; Davis, Barrett, et al., 2020; Davis, Xin, et al., 2023; Davis, Xin, et al., 2021; Mangini et al., 2022). Psychological flexibility involves six core processes: acceptance, cognitive defusion, being present, self as context, values and committed action (Watts & Luoma, 2020). Of these, cognitive defusion is considered central to fostering psychological flexibility. The opposite of cognitive defusion is cognitive fusion. Cognitive

fusion is a state where an individual is entangled with their thoughts, treating them as literal truths rather than mental events, which can lead to rigid behavior patterns, experiential avoidance, and emotional distress (Gillanders et al., 2014). Because there is an inverse relationship between higher levels of cognitive fusion and lower psychological flexibility, in Manuscript 1, I aimed to investigate the potential psychological mechanisms underlying the therapeutic effects of 5-MeO-DMT with a main focus on cognitive fusion.

Findings from this study preliminarily support the hypothesis that decreases in cognitive fusion from before-to-after 5-MeO-DMT use may underlie increases in psychological flexibility and its consequent positive mental health effects across diagnoses documented to date (Davis, Averill, et al., 2020; Davis, Timmermann, et al., 2023; Davis, Xin, et al., 2021; Mangini et al., 2022).

Given the transdiagnostic value attributed to psychedelics (Kočárová et al., 2021), the theoretical relevance of the psychological flexibility model in psychedelic research (Luoma, Davis, et al., 2020), and the findings from Manuscript 1, it is plausible that reductions in cognitive fusion are part of a central mechanism by which psychedelics produce therapeutic effects across diagnoses. Decreases in cognitive fusion were associated with greater ratings of challenging experiences and psychological insight. Ego-dissolution, while not associated with these decreases, were, on the other hand, associated with greater ratings of persisting positive effects attributed to the 5-MeO-DMT experience.

While both the OLS and Tobit models examining the associations between persisting effects and ego dissolution exhibited problems with residuals, suggesting deviations from normality, and thereby questioning the validity of this finding, Tobit models are robust enough to accommodate such non-normality (Cunillera, 2014). Furthermore, from a subject matter

perspective, the censored or truncated nature of the data – where 20 of the 90 respondents reported the highest possible score (33) and one respondent reported the lowest possible score (-33), with only a few near the lower end and most clustering close to the highest score – actually seems to mirror real-life experiences. This distribution reflects the reality that while the majority of individuals report incredible benefits and regard their 5-MeO-DMT experience as one of the most transcending and transformative experiences of their lives, a small percentage encounter extremely negative experiences. This characteristic of the data can be seen as a hidden strength within the study's limitations, as it may authentically represent the diverse range of responses to 5-MeO-DMT use.

This data trend is what may, at least in part, be reflected in the findings from Manuscript 2, which examined the commonly occurring phenomenon of reactivation associated with 5-MeO-DMT use in naturalistic settings. A prior study on reactivations reported that only 3% and 7% from two different subsamples described the emotional valence of these reactivations as negative. Manuscript 2 aligns with these findings, with 3% of the sample reporting reactivations as negative experiences.

Given the growing interest in developing 5-MeO-DMT as an approved mental health treatment (Aday et al., 2023), and considering the currently limited knowledge regarding reactivations, Manuscript 2 sought to expand our understanding of the phenomenon by examining its prevalence rates, predictors and attributed emotional valence among a sample of Spanish-speaking individuals. A novel finding of this study was that decreases in cognitive fusion were associated with greater likelihood of reactivation events, and psychological insight was associated with positive valence of these experiences when they occurred. This study replicated the prior finding of longer planning times as part of a preparation process for a 5-

MeO-DMT experience being predictive of reactivations, suggesting that intentional preparation may play a role in facilitating reactivations, reducing the likelihood of negatively valenced experiences, and optimizing treatment effects.

Naturalistic survey data reflect real-world use of 5-MeO-DMT, capturing a broad range of experiences and outcomes that may not be fully represented in controlled clinical settings. Insights from survey studies, such as this, can inform the development of trial protocols. The data on reactivations presented herein can help tailor interventions to individual patient needs, optimizing therapeutic outcomes by addressing specific predictors of positive or negative reactivations. Further research in ongoing and future clinical trials of 5-MeO-DMT as a mental health treatment should explore the mechanisms by which decreases in cognitive fusion and psychological insight contribute to the likelihood of reactivations occurring, and how they might map out to clinical outcomes long-term based on their emotional valence.

The historical and ethnocultural contexts of 5-MeO-DMT use provide essential insights into its therapeutic potential and societal impact. Manuscript 3 delved into the uses of 5-MeO-DMT by various Indigenous tribes in ancient and, in some cases, present South America (e.g., the Yanomano). One common thread among these uses is that, regardless of whether it is called *cohoba, vilca, yopo, epéna,* or any other of the numerous names used to refer to 5-MeO-DMT-containing snuffs by various Indigenous groups, all the way from Argentina, Chile, Bolivia, Peru, Colombia, Venezuela, and including the Caribbean Islands as documented by Pané in 1496, 5-MeO-DMT was employed for divination, diagnosing and healing, to communicate with ancestors and deities, as a rite of passage, to address conflicts, to promote community bonding, among others (Schultes, 1979; Torres & Repke, 2006).

This raises the questions: How might these ancient uses inform today's best practices for 5-MeO-DMT administration and facilitation? What might this teach us about how to best establish systems of delivery of care utilizing this substance? What is the value of administering it in individual settings with two facilitators to promote personal healing as is most often done in psychedelic research trials, as opposed to in group settings with the intention to promote community bonding and healthy conflict resolution? How can Indigenous-inspired practices be integrated into Western research contexts and clinical facilitation in ways that instead of being about cultural appropriation, are about cultural appreciation and respect. All these are questions worthy of rigorous scholarly examination. Celidwen and colleagues (2023) have begun a conversation related to some of the answers to these questions. They emphasize the importance of integrating ethical principles from traditional Indigenous medicine into Western psychedelic research and practice: Reverence, Respect, Responsibility, Relevance, Regulation, Reparation, Restoration, and Reconciliation (Celidwen et al., 2023). These principles can guide the development of culturally sensitive and ecologically sensitive novel psychedelic treatments.

In Manuscript 1 (Chapter 2), Model 2 analyses revealed that respondents who used 5-MeO-DMT for spiritual exploration experienced larger increases in nature relatedness and prosocial behavior compared to those who used it for personal growth or experimentation reasons. Historically, 5-MeO-DMT was used in communal and spiritual contexts to foster a sense of connection to the natural world, the community, and the spiritual realm. In this sense, the study's finding suggest that when 5-MeO-DMT is used with the intention of spiritual exploration, it may enhance feelings of interconnectedness (Kałużna et al., 2022; Watts et al., 2022) and prosocial behavior, similar to the experiences of Indigenous peoples.

In this vein, the traditional group settings used in Indigenous cultures for communal bonding and conflict resolution purposes might offer valuable insights for modern therapeutic practices and applications. Incorporating elements of these communal ceremonies could enhance the therapeutic benefits of 5-MeO-DMT, potentially enhancing interpersonal relationships and fostering well-being thru increased social connectedness, which is a biological imperative for humans (Porges, 2022).

Besides offering a comprehensive overview of traditional uses of 5-MeO-DMT in ancient South America, Manuscript 3 addressed elements of a pervasive toad motif present in Mesoamerican art and culture. This motif has been extensively associated with the symbolic cycles of rain, regeneration and fertility among the Aztecs, Mayans, and Olmecs (Cyphers et al., 2005; Kennedy, 1982; Smith, 2011). In the most recent decade, however, this motif has been coopted to suggest that these civilizations utilized toad-derived 5-MeO-DMT in ceremonial contexts (Horák et al., 2019), and that the Comcaac people of the Sonoran Desert also used to smoked toad secretions in ceremonial contexts in ancestral times. The word *otac* has become synonymous with this alleged toad smoking ceremony practiced by the Comcaac Indians in Sonora. However, recent documentation (de Greef, 2022; Ogarrio Huitrón, 2022), and Manuscript 3 (Chapter 4) observed that there is no robust evidence to support these claims. As Felger and Moser documented in their extensive ethnographic work about the Comcaac, “amphibians were inconsequential” to the Comcaac Indians (Felger & Moser, 1985).

At present time, there is a growing divide between individuals and organizations that insist on using toad secretions, often creating churches to declare the secretions their sacrament (Romero, 2022), and those who advocate for the use of synthetic versions of 5-MeO-DMT (Morris, 2021; Sherwood et al., 2020). The stance of insisting on using natural toad secretions

overlooks significant ecological concerns (Villa, 2023). The demand for toad secretions has led to the exploitation and endangerment of the *Incilius alvarius* toad (Peterson, 2023), which is contradictory to the values of nature relatedness and prosocial behavior. There is an ecological blind spot in the insistence of using toad secretions. To reconcile the spiritual and psychological benefits of 5-MeO-DMT with ecological responsibility, it is crucial to advocate for the use of synthetic 5-MeO-DMT (Villa, 2023). Synthetic versions provide comparable therapeutic benefits without causing harm to natural toad populations and their ecosystems. Future research should focus on educating the community about the ecological impacts of using toad secretions and promoting the adoption of synthetic 5-MeO-DMT.

In conclusion, this dissertation has provided a comprehensive exploration of 5-MeO-DMT from multiple perspectives, addressing possible mechanisms of therapeutic action, reactivations, and historical and cultural considerations. Collectively, these studies underscore the multifaceted nature of 5-MeO-DMT, offering valuable insights for its development as a mental health tool, while advocating for sustainable and culturally sensitive practices.

Furthermore, this dissertation emphasized the importance of including Spanish-speaking populations in psychedelic research. The cultural and linguistic diversity of participants can provide more comprehensive understanding of the therapeutic effects of psychedelics like 5-MeO-DMT. By addressing the unique experiences and contexts of Spanish-speaking individuals, this research contributes to the development of more inclusive and culturally sensitive therapeutic practices. Expanding the scope of psychedelic studies to encompass a broader range of cultural backgrounds is essential for the equitable advancement of this field and for maximizing the therapeutic potential of these substances across diverse populations.

"It is imperative that we learn how to implement optimal models for administering such powerful compounds as 5-MeO-DMT. The question now before us is whether we as a society have sufficiently evolved so that we are able to contain and support investigations of this vital yet long-neglected field."

-Dr. Charles Grob

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