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Psychedelic Therapy as Relational Medicine: Psychosocial Mechanisms in Clinical and Naturalistic Contexts

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Supervised by Robin Carhart-Harris and David Erritzoe

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Statement of Publications

The data presented in Chapter 3 were published in similar form in *Frontiers in Pharmacology* (Murphy et al., 2022):

- Murphy, R., Kettner, H., Zeifman, R., Giribaldi, B., Kartner, L., Martell, J., ... & Carhart-Harris, R. (2022). Therapeutic alliance and rapport modulate responses to psilocybin assisted therapy for depression.

Chapter 4 combines results published in similar form in *Frontiers in Pharmacology* (Kettner et al., 2021), *Nature Scientific Reports* (Timmermann et al., 2021), *Pharmacology* (Watts et al., 2022*),* and the *American Journal of Geriatric Psychiatry* (Kettner et al., 2024):

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- Timmermann, C., Kettner, H., Letheby, C., Roseman, L., Rosas, F. E., & Carhart-Harris, R. L. (2021). Psychedelics alter metaphysical beliefs.
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Declaration of Originality

Chapter 3 includes secondary analyses that were performed on data collected as part of the 'Psilodep 2' randomized clinical trial (RCT), which was conducted and first published by Robin Carhart-Harris, Bruna Giribaldi, Rosalind Watts, Michelle Baker-Jones, Ashleigh Murphy-Beiner, Roberta Murphy, Jonny Martell, Allan Blemings, David Erritzoe, and David J. Nutt (2021).

The design of the observational study presented in Chapter 4 was developed in collaboration with Robin Carhart-Harris and Leor Roseman. Item pools for the Communitas Scale (COMS), Watts' Connectedness Scale (WCS), and Metaphysical Beliefs Questionnaire (MBQ) were developed in collaboration with Leor Roseman, Rosalind Watts and Christopher Timmermann. The psychometric validation of these measures, as well as any included statistical analyses and their interpretation are my own.

The group-based VR intervention presented in Chapter 5 is based on software originally created and validated by David Glowacki et al. (2020), which was further developed and integrated into a multi-week program by staff members of aNUma, Inc., a public benefit corporation registered in San Rafael, California. The program under study was carried out by staff associated with aNUma, Inc., including Justin Wall and Joseph Hardy, who also collaborated on the design and data collection of the presented observational study.

The work reported in this thesis is my own and all else is appropriately referenced, in line with the rules and guidelines set out for PhD theses by Imperial College London.

Abstract

This thesis explores the psychosocial mechanisms underlying therapeutic responses to psychedelic interventions, advancing an enactive biopsychosocial perspective that foregrounds dynamic and reciprocal causal relationships between biological, psychological, and social processes. While clinical studies increasingly demonstrate the efficacy of serotonergic psychedelics for a range of mental health conditions, the contribution of relational factors - such as therapeutic alliance, group dynamics, and socially enriched settings - remains insufficiently understood. To better characterize the role of psychosocial dynamics, three empirical studies were conducted across clinical, naturalistic, and digitally mediated settings.

Study 1 (Chapter 3) analysed data from a randomized controlled trial comparing psilocybin with escitalopram, demonstrating that therapeutic alliance predicted depression outcomes in the psilocybin arm, mediated by the quality of acute subjective psychedelic effects. Study 2 (Chapter 4) examined data from naturalistic psychedelic group experiences, identifying 'communitas', a transient state of intense togetherness and shared humanity, as a key predictor of enduring improvements in well-being and connectedness, and shifts in metaphysical beliefs. Study 3 (Chapter 5) evaluated a group-based virtual reality program leveraging psychedelic-like states, finding positive psychological effects in participants with life-threatening illnesses, underscoring the relevance of context even in non-pharmacological psychotropic interventions.

Together, these findings suggest that rather than functioning solely as biomedical interventions, psychedelics may act as amplifiers of relational processes and be best understood as hybrid pharmaco-psychosocial interventions. This work supports the clinical integration of psychedelics as part of psychosocially enriched therapeutic paradigms and contributes to broader debates about the role of relational context and intersubjectivity in mental health care.

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Chapter 1: Background - A Biopsychosocial Perspective on Psychedelic Effects

The contemporary resurgence of interest in psychedelic therapy is often described as a resumption or 'renaissance' of the mid-20th-century research program, centred on the psychiatric application of lysergic acid diethylamide (LSD) (Belouin & Henningfield, 2018; Sessa, 2018). When examining the treatment models applied in modern psychedelic trials, it becomes clear that this historical frame of reference is more than just rhetorical: Now, as then, the practice of psychedelic therapy includes not only the administration of a drug, but also the intentional curation of various 'extrapharmacological' factors - the 'set and setting' of drug administration. Recognized already by early LSD research pioneers as a crucial determinant of psychedelic drug effects (Hartogsohn, 2017; Hyde, 1960; Leary, 1961), non-drug components of psychedelic interventions typically include music, aesthetic alterations to the dosing space, and importantly, the provision of psychological support throughout dosing, preparation, and follow-up integration sessions (Chisamore et al., 2024; Horton et al., 2021).

Throughout the decades-long hiatus of psychedelic research, the psychosocially enriched structure of psychedelic therapy has largely been conserved, thanks in no small part to the continued influence of a few singular scholars (Doblin, 2015; Grof et al., 1973; Meckel, 2019; Richards, 2015) and explains why psychedelic therapy is also referred to as psychedelic-assisted therapy (PAT) or psychotherapy (PAP). However, while contemporary psychedelic research continues to yield groundbreaking insights into the neurobiological mechanisms underlying psychedelic drug action (Carhart-Harris & Nutt, 2017; De Vos et al., 2021; Vollenweider & Kometer, 2010; Vollenweider & Preller, 2020), the contribution of psychosocial factors in shaping psychedelic effects remains largely underexplored (Aday et al., 2024; Bassir Nia et al., 2025).

The present research aims to address the knowledge gap surrounding psychosocial mechanisms hypothesized to underlie psychedelic drug effects. To do so, Chapter 3 will present evidence from a randomized controlled trial (RCT) of psilocybin for major depression, examining how therapeutic alliance and rapport influence acute psychedelic effects and, in turn, shape symptom trajectories. Next, Chapter 4 widens the scope beyond clinical settings by exploring naturalistic group contexts of psychedelic use. This observational study introduces and psychometrically validates a novel measure of psychedelic *Communitas*, an intense state of sharing and togetherness, assessing its predictive value for enduring changes in psychological well-being, social connectedness, and metaphysical beliefs. Finally, Chapter 5 further expands the inquiry to include non-pharmacological interventions, presenting findings from an open-label pilot study evaluating a psychedelic-inspired, group-based virtual reality program designed to support patients with life-threatening illnesses.

But first, the following introductory chapter will provide a review of prior research on psychedelic effects and their putative biological, psychological, and social mechanisms. It aims to conceptually anchor the presented findings in the existing literature describing psychosocial contributions to both behavioural as well as pharmacological therapies, arguing for the value of a biopsychosocial perspective on psychedelic effects.

1.1 Defining Psychedelics in a Shifting Psychiatric Landscape

To fathom hell or go angelic, just take a pinch of psychedelic

- Letter from Humphrey Osmond to Aldous Huxley (1956)

Between etymology and pharmacology. The Term ‘psychedelic’ combines the Greek words psykhē ("mind" or “soul”) + dēloun ("make visible”, “reveal", “manifest”) and first

appeared in a 1956 letter from the psychiatrist Humphrey Osmond to the author Aldous Huxley (Bisbee et al., 2018). In the first scholarly article that introduces the term, Osmond (1957) intended to put forth a more inclusive alternative to the then used term 'psychotomimetic', marking a shift away from the original use of LSD to study model psychoses, to the notion that LSD and related substances may offer therapeutic utility, specifically in psychotherapy and -analysis. Osmond counted a range of psychoactive plants and substances among the psychedelics that have since been revealed to constitute agonists of the serotonin 2A receptor (5-HT2AR), including the tryptamine alkaloids dimethyltryptamine (DMT, mentioned by Osmond as 'Syrian Rue' and '*Virola* snuff'), bufotenine (in 'Cohoba', the ground seeds of *Anadenanthera peregrina*), and psilocybin (specifically, 'fungus teonanacatl', i.e. *psilocybe mexicana*); the phenethylamines mescaline (including the 'peyote cactus') and the synthetic trimethoxyamphetamine (TMA); as well as the ergolines ergine (LSA, derived from 'ololiuqui', i.e. *Ipomoea corymbosa* seeds, a species of morning-glory flower) and of course LSD. However, Osmond also included substances that are now known to not primarily act as 5-HT2AR agonists: Ibogaine ('iboga bean'), cannabinoids ('hashish'), harmala alkaloids ('caapi vine', possibly included by Osmond due to its use in conjunction with the DMT-containing leaves of *psychotria viridis* in form of Ayahuasca); the dopaminergic adrenaline-derivatives adrenochrome and adrenolutin, and the Gamma-Aminobutyric Acid (GABA) and N-methyl-D-aspartic acid (NMDA) agonists muscimol and ibotenic acid (in 'amanita pantherina' and 'amanita muscaria', commonly known as the fly agaric mushroom).

Osmond's receptor-agnostic definition of psychedelics was based on their reported psychoactive properties and without doubt at least partially owed to the limited knowledge of cellular pharmacology at the time. Regardless, contrary to claims recently made in an attempt to historically justify a more exclusive definition of the term 'psychedelic' as primary 5-

HT2AR agonists (Nichols et al., 2023), Osmond never used the term exclusively for the 5-HT2A agonists LSD, mescaline, and psilocybin, directly. This illustrates how the boundaries of the term 'psychedelic' remain subject to contemporary scientific debate, further complicated by recent proposals for "non-hallucinogenic" (Cameron et al., 2021) and, oxymoronically, "non-psychedelic" psychedelics, i.e. 5-HT2AR agonists without psychoactive effects. Recognizing the utility of a distinction between 'classic psychedelics' (5-HT2AR agonists) and 'non-classic' or 'atypical' psychedelics, which include substances used in settings that resemble psychedelic therapy, such as 3,4-Methylenedioxymethamphetamine (MDMA) and ketamine, the present thesis, unless otherwise specified, will use the term 'psychedelic' exclusively in reference to psychoactive 5-HT2AR agonists such as psilocybin and LSD. Nevertheless, it should be noted that the conceptual and phenomenological overlap between various forms of metacognitively insightful or 'mind-revealing' (etymologically, *psychedelic*) experiences—regardless of their mode of induction—has been strategically harnessed by other interventions, such as virtual reality (Kaup et al., 2023), a connection that will be further explored in Chapter 5.

Psychedelics amid psychiatry's reductionist drift. The ongoing terminological dispute regarding psychedelics is reflective not only of their multidisciplinary appeal (Bartlett et al., 2023), but also of an underlying ideological divide within contemporary psychiatry. Parallels can be drawn between the argument for a biochemically derived definition of psychedelics and biochemically derived definitions of mental health and illness, which have come to dominate theory and practice in psychiatry. The relative stasis of psychedelic research throughout its decades-long hiatus - precipitated by the 1971 Controlled Substances Act - stands in stark contrast to the transformations that reshaped its parent discipline. A 'psychopharmacological revolution' in psychiatry unfolded regardless, triggered not by psychedelics, but by the

introduction of novel antipsychotics (Lehmann & Hanrahan, 1954; López-Muñoz et al., 2005), tricyclic antidepressants (Brown & Rosdolsky, 2015; Lehmann & Hanrahan, 1954), and eventually, selective serotonin re-uptake inhibitors (SSRIs) (Lemberger et al., 1978; Owens, 2004), which remain first-line treatment for depression. As a result, at the level of clinical practice, the percentage of patient visits to psychiatrists involving psychotherapy has halved since 1996 in the US (Tadmon & Olfson, 2022), with more than half of psychiatrists no longer offering it at all. While short medication management visits are economically attractive (West et al., 2003), their prioritization contradicts meta-analytic evidence (Cuijpers et al., 2020; Kamenov et al., 2017; Leichsenring et al., 2022; Spielmans et al., 2011) and patient preferences for psychotherapy and combined treatments over medication (McHugh et al., 2013). At a conceptual level, psychiatry's biomedical revolution has marginalized perspectives emphasising social and cultural dimensions of mental health (Deacon, 2013; Kirmayer & Gold, 2011), a trend that has been identified to extend also to the new wave of psychedelic research (Davies et al., 2023; Gearin & Devenot, 2021; George et al., 2020; Noorani, 2020).

It is against this backdrop that the potentially disruptive value of the psychosocially enriched structure inherent to psychedelic-assisted interventions emerges. Unlike conventional psychopharmacological treatments, psychedelic therapy is being developed as a functionally integrated psychopharmacological-psychosocial intervention. As such, psychedelic research has been recognized for its inherent potential to bridge and reconcile neurobiological and psychosocial perspectives (Aicher et al., 2024; Gobbi et al., 2022; Greenway et al., 2020; Gründer et al., 2024). The following section will situate this opportunity within a broader theoretical framework – the biopsychosocial model (BPSM) - established by George Engel in 1977 with a similar objective, that is to reintegrate psychosocial concepts into biomedical discourse and psychiatric practice.

1.2 The Biopsychosocial Model: Origins and Contemporary Relevance

Health is a state of complete physical, mental, and social well-being […]

Constitution of the World Health Organization (1947)

Emergence of a new model. Although the BPSM has since become synonymous with George Engel's (1977) effort to counterbalance reductionist biomedical conceptions of health, the term 'biopsychosocial' was first coined 25 years earlier from the contrary perspective, when the neurologist and psychiatrist Roy Grinker (1966, 1994) foresaw the need for an explanatory device that could integrate novel bioscientific insights into the psychoanalytically dominated field of psychiatry. Approaching from the opposing starting point, Engel's (1977) programmatic publication had a similar goal, i.e. developing holistic conceptions of health and illness that could account for biological, psychological, and social causes. Engel drew from Bertalanffy's (1968) General Systems Theory as a potential framework to formalize the reciprocal causal relationships between components of different explanatory levels, organized in a hierarchically nested structure of interacting dynamic systems (George & Engel, 1980, see also Figs. 1.1, 1.2 below). According to the BPSM, the interconnectedness between systems of different levels entails that disruptions necessarily manifest on all levels, from the smallest, molecular level to the largest, societal and biospheric levels. A disruption observed on any one level (e.g., in form of a discrete behavioural psychopathology) can thus be best understood using a pluralistic, multifactorial approach to its causation.

The fundamentally multidisciplinary nature of its core tenet has allowed the BPSM to garner support from diverse lines of evidence, establishing it as the most widely accepted non-reductionist model in modern medicine. In its inception, it addressed the limited ability of purely biomedical perspectives to address psychosomatic conditions where biological pathology alone seemed insufficient to explain symptoms or treatment outcomes (Lipowski,

1988). Later, the BPSM became helpful explaining evidence of placebo and nocebo effects, which demonstrated that psychological and social factors, including beliefs, expectations, and social context, could directly influence physiological reactions to treatments, such as the release of endogenous opioids in placebo analgesia (Benedetti, 2006, 2013; Wager et al., 2007). The BPSM has since been evoked in relation to numerous highly influential concepts, such as the diathesis-stress model (Schotte et al., 2006; Wong, 2014) gene-environment interactions (Rolland & Williams, 2005), and epigenetics (Yehuda et al., 2016; Yehuda & Flory, 2018), among others.

Recent applications of the BPSM. Relevant to contemporary psychedelic research, the application of the BPSM has proven particularly fruitful at the intersection of psychopharmacological and psychosocial research within psychiatry. Demonstrating the contribution of non-pharmacological factors to psychopharmacological treatments, meta-analyses have attributed 50-80% of the therapeutic response to antidepressant treatment to placebo effects (Kirsch et al., 2008; Kirsch et al., 2002; Rief et al., 2009), which have been found to share common neural pathways, e.g., in their effect on cortical glucose metabolism (Mayberg et al., 2002). Importantly, the response to antidepressants, but also to active and passive placebo treatment has been shown to be affected by the level of therapeutic alliance between patients and clinicians (Leuchter et al., 2014; Zilcha-Mano et al., 2015). In one study the amount of variance explained was at a level comparable to patients receiving psychotherapy (Krupnick et al., 2006). Outcomes of antidepressant treatment have also been found to differ depending on factors such as socioeconomic background, education, income, and employment status (Chiarotti et al., 2017; Viglione et al., 2019), indicating that the effects of antidepressants may partially be explained by their ability to increase the sensitivity to existing living

conditions, which would amount to an interaction between biological and social causes affecting psychological outcomes.

Conversely, psychosocial interventions such as cognitive behavioural therapy (CBT) and other forms of psychotherapy have been shown to produce various physiological responses in humans that partially explain their therapeutic effects. For example, positive response to CBT for depression has been found to be associated with increased serotonin transporter binding, suggesting enhanced serotonergic activity (Amsterdam et al., 2013). Changes in regional brain activity and functional connectivity following psychotherapy often implicate the cognitive control network (Shou et al., 2017) and its connectivity to the amygdala (Shou et al., 2017), although results have been less consistent and shown to differ depending on the psychiatric disorder and form of psychotherapy employed (Barsaglini et al., 2014). Psychotherapy has also been found to affect gene expression, DNA methylation and other epigenetic markers that have previously been related to psychopathology (Perroud et al., 2013; SNM et al., 2020; Yehuda et al., 2013).

In summary, the therapeutic effects of conventional psychosocial and pharmacological treatments may be less distinctly attributable to either psychosocial or pharmacological causes than they initially appear. The BPSM offers a useful framework for understanding the interplay between biological, psychological, and social determinants of health, including outcomes of psychiatric interventions. The following section will explore how psychedelic effects can be interpreted from a biopsychosocial perspective, using a modernized version of the BPSM that incorporates enactivist principles, aiming to establish a conceptual foundation for the overarching research objective, i.e. to investigate the role of psychosocial factors in psychedelic drug action.

1.3 An Enactive Biopsychosocial Perspective on Psychedelic Effects

To come very near to a true theory, and to grasp its precise application, are two different things, as the history of science teaches us. Everything of importance has been said before by someone else who did not discover it.

Alfred North Whitehead (1917)

Current explanatory models of psychedelic effects. Several unifying explanatory models of psychedelic effects have been proposed in the past (for a review, see Swanson, 2018). First introduced to replace the then prominent psychotomimetic approach, Osmond (1957) and Huxley explained the effects of psychedelics employing an older model of the brain as a filtration device for consciousness (James, 1890; Myers, 1904), metaphorically, a 'cerebral reducing valve' (Huxley, 1962). In this model, the brain's function is to reduce or filtrate the vast scope of possible sensory experience into a focused stream of consciousness based on "biologically useful and socially conditioned perceptions, thoughts and feelings" (Huxley, 1961). In this analogy, Osmond and Huxley argued that psychedelic substances would temporarily open this reducing valve, allowing more of reality, an "[…] other world to rise into consciousness" (Huxley, 1999).

Despite being more hermeneutically than empirically derived, the model intuited by Huxley and Osmond continues to have a surprisingly large degree of relevance in face of novel neuroscientific insights. Specifically, the idea that psychedelics work by reducing constraints in the processing of sensory (or more generally, bottom-up) information lives on in contemporary unifying theories of psychedelic action. For example, according to the cortico-striato-thalamo-cortical model (CSTC), Vollenweider and Geyer (2001) suggest that psychedelics "reduce the sensory gating systems of the lower brain structures, leading to a

flood of information into higher levels of the brain". Localizing the 'reducing valve' in a specific brain area, the gating function of the thalamus thereby becomes the core of the CSTC. The underlying process is thought to be initiated through a series of feedback loops originating at medial prefrontal layer V pyramidal neurons, ultimately causing disinhibition of thalamic gating and flooding the cortex with sensory information. Although evidence for the CSTC model has been mixed, it remains one of several leading models of psychedelic brain effects to date (Doss et al., 2022; Melani et al., 2025).

Carhart-Harris and Friston (2019) provide another formalization and neurocomputational expansion on the idea of the reducing valve with the relaxed beliefs under psychedelics model (REBUS). Drawing from predictive coding and Bayesian brain frameworks, REBUS suggests that "the highest level of the brain's functional architecture ordinarily exerts an important constraining and compressing influence on perception, cognition, and emotion" and "suggest that psychedelics impair this compressive function, resulting in a decompression of the mind-at-large" (Carhart-Harris & Friston, 2019). By disrupting hierarchical constraints within the brain, REBUS proposes that psychedelics induce a state of cognitive and perceptual openness, less constrained bottom-up information flow, and enhanced susceptibility to enduring psychological and neurobiological changes. Drawing from predictive coding and Bayesian principles of belief updating, REBUS predicts that by relaxing the precision of high-level priors or beliefs, psychedelics enable increased bottom-up information flow and render deeply held assumptions more flexible for revision.

Importantly, the central role of liberated bottom-up information flow purported similarly by the CSTC model, the reducing valve model, as well as its refined and expanded neurocomputational formulation within REBUS can readily be integrated into a

biopsychosocial account of psychedelic effects. Each of these theories entail a sensitization to context, including also in its psychosocial and ultimately even cultural dimensions. For example, Carhart-Harris and Friston (2019) acknowledge how REBUS recognizes the crucial importance of context for the therapeutic efficacy of psychedelics: "psychedelics work to relax high-level priors, sensitizing them to liberated bottom-up information flow, which, *with the right intention, care provision and context*, can help guide and cultivate the revision of entrenched pathological priors." [highlight mine].

Enactivism and circular causality. Meling and Scheidegger (2023) have recently offered an expansion on existing unifying models of psychedelic action based on the principles of enactivism, a theoretical framework in cognitive science and philosophy of mind that emphasises the active, embodied, and embedded nature of cognition (Colombetti & Thompson, 2007; Di Paolo & Thompson, 2014; Varela et al., 2017). Meling and Scheidegger explain the relationship between psychedelic substances, brain activity, and subjective experience using the concept of reciprocal or circular causality, i.e. the notion that these systems influence each other bidirectionally, rather than in a linear or integrative process. This enactive conception of psychedelic effects emphasises how "change in one's biological state (for example, by a psychedelic drug) may result in […] changes in one's experiential state" while at the same time recognizing that "intervening on one's experience has consequences on one's biological state". Through the concept of circular causality, enactivism thus provides an explanation for how different levels of the BPSM may causally interact (Borrell-Carrió et al., 2004; De Haan, 2021), constituting an important modernization of the BPSM (Cormack et al., 2023; Noble et al., 2019).

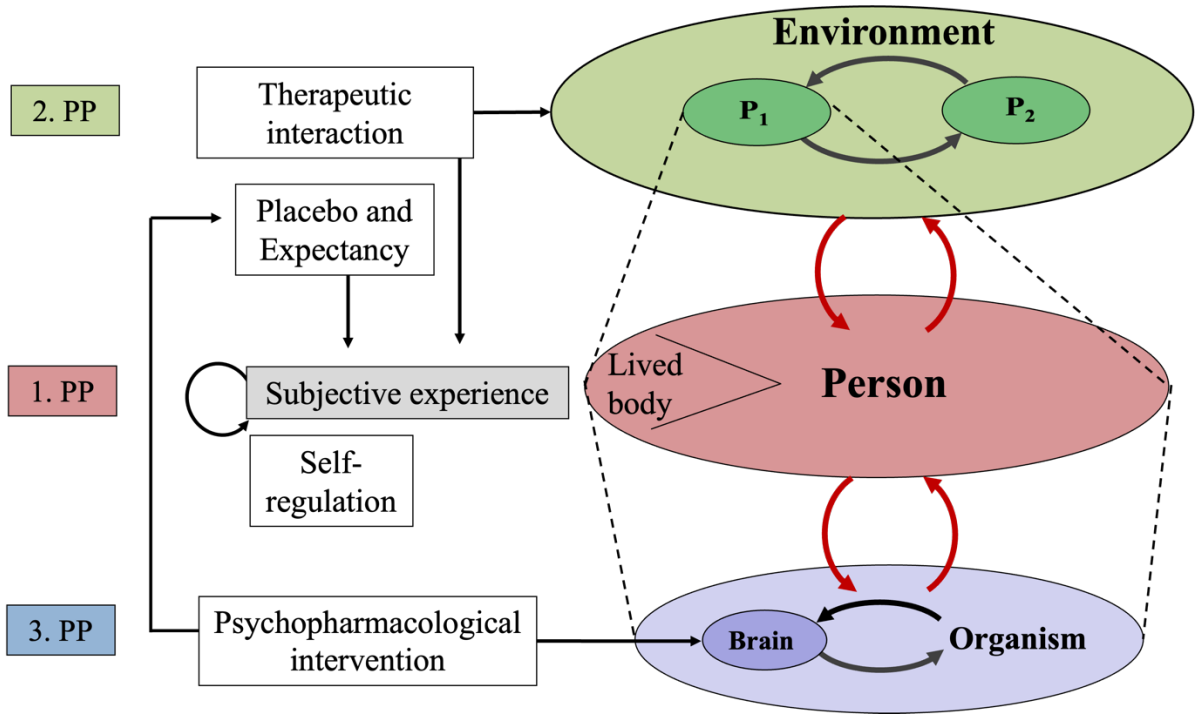


Figure 1.1 Psychedelic Effects from an Enactive Perspective. Circular causal processes mediate interactions between physiological processes, accessible using a 3rd person perspective (3. PP); subjectively experienced and embodied drug effects (1. PP); social interaction and intersubjective experience (2. PP). Adapted with permission from Fuchs (2023).

In addition to the introduction of circular causal relationships, enactivism introduces an emphasis on the lived experience of the subject, emerging as a dynamic interaction between organism and environment, making it a particularly suitable framework to explain the relational nature of psychiatry (De Haan, 2020a; Fuchs, 2023), but also the role of set and setting for psychedelic drug experiences. Fuchs (2023, Figure 1.1) provides a multilevel view of circular processes within psychiatric interventions, which illustrates how causality in psychosocial and pharmacological interventions may be understood within the same framework of circular brain-person-environment feedback loops. The following sections aim to present evidence of such reciprocal causal relationships within and between system levels while summarizing the biological, psychological, and social factors that have been studied in relation to the effects of psychedelic interventions, intending to illustrate the value of a pluralistic, multidimensional

view of causation embedded within the larger scope of the BPSM (Meling & Scheidegger, 2023; van Elk & Yaden, 2022).

1.3.1 Biological Processes

Molecular and cellular effects. While psychedelics, like most drugs, can be introduced to the human body in a variety of ways, the most common route of administration in contemporary research is *per os*. Using the example of psilocybin, the drug must first undergo a series of physiological processes that facilitate its entry into the brain, ultimately allowing it to exert its psychoactive effects. Upon oral ingestion, psilocybin enters the gastrointestinal tract, where it undergoes passive diffusion into capillaries within the small intestine. At this point already, a reciprocal causal dynamic between drug and user can be identified, insofar as psilocybin's affinity to serotonin receptors in the gut can produce a systemic and embodied response in form of nausea and emesis, common side-effects of psilocybin ingestion (Breeksema et al., 2022), that enable the body to curtail further drug effects. From the small intestine, psilocybin is transported through the hepatic portal veins to the liver, where it undergoes first-pass metabolism. Within the cells of the liver, it is dephosphorylated by the enzyme alkaline phosphatase and converted into its active metabolite, psilocin (Hasler et al., 1997; Passie et al., 2002). Once metabolized, psilocin enters systemic circulation through the inferior caval vein, reaching the heart, which subsequently distributes it throughout the body, including the central nervous system. It is only through the removal of psilocybin's hydrophilic phosphate group during metabolism, that psilocin's greater lipophilicity allows for transport through the lipid-rich blood-brain barrier; to unfold its potentially transformative psycho- and biological effects on the user, psilocybin thus needs to first be transformed itself – a foundational example of a reciprocal interaction on the organismic-molecular level.

After passing the blood-brain barrier, psilocin diffuses into the extracellular space of the brain, traveling freely between neurons and binding to its target receptors. Psilocin, like other serotonergic psychedelics, interacts with a broad range of serotonin receptor subtypes, including 5-HT1A, 5-HT2B, and 5-HT2C receptors, but its psychoactive effects are primarily mediated by the 5-HT2AR (Glennon et al., 1984; Vollenweider et al., 1998). Recent findings suggest that both extracellular and intracellular variants of the 5-HT2AR contribute to its functional effects (Vargas et al., 2023). The 5-HT2AR is expressed widely throughout the human brain, but most densely in cortical areas - especially high level and evolutionarily recent transmodal associative areas such as the medial prefrontal cortex or the anterior cingulate cortex, parts of the default mode network (DMN) (Beliveau et al., 2017). Within these areas, the 5-HT2AR is primarily found on the apical dendrites of glutamatergic layer 5 pyramidal neurons (López-Giménez et al., 2001) and to a lesser extent on GABAergic inhibitory interneurons (De Almeida & Mengod, 2007).

Their structural similarity to serotonin allows classic psychedelics, such as psilocin, LSD, and DMT, to bind to the orthosteric binding site of the 5-HT2AR as high-affinity partial agonists. Upon binding, a conformational change in the receptor is induced, leading to the exposure of an intracellular G-protein binding interface, which facilitates downstream signalling cascades, involving the activation of phospholipase Cγ and the subsequent release of intracellular calcium from the endoplasmic reticulum through inositol trisphosphate. The phospholipase Cγ pathway also produces diacylglycerol, which in turn triggers the activation of protein kinase C and various interconnected downstream pathways, ultimately resulting in neuronal firing through membrane depolarization and diminished afterhyperpolarization (Banerjee & Vaidya, 2020; Egan et al., 2000). Indeed, 5-HT2AR activation, including by psychedelics, has reliably been found to increase the frequency and amplitude of glutamatergic

signalling in layer 5 pyramidal cells (Aghajanian & Marek, 1997; Aghajanian & Marek, 1999; Celada et al., 2008; Marek, 2018; Schmitz et al., 2022; Sipes & Geyer, 1995), with one magnetic resonance spectroscopy study linking this increase in glutamatergic activity to psilocybin's acute subjective effects in humans (Mason et al., 2020).

Beyond 5-HT2AR agonism, several psychedelics, including psilocybin, have also been found to act as allosteric modulators of tropomyosin receptor kinase B, a receptor for the brain-derived neurotrophic factor (BDNF) (Moliner et al., 2023), partially explaining the well-documented neuroplastic effects of classic psychedelics (Berthoux et al., 2019; Jones et al., 2009; Ly et al., 2018). While the therapeutic role of psychedelic-induced neuroplasticity remains difficult to demonstrate in humans, increased BDNF levels have been identified as a marker of response to conventional antidepressants, ketamine (Björkholm & Monteggia, 2016), and electroconvulsive therapy for depression (Rocha et al., 2016). Importantly, however, neuroplasticity, including psychedelic-induced neuroplasticity, should not be considered inherently positive or therapeutic (Artin et al., 2021; Brown & Weaver, 2012). Evidence of aberrant or maladaptive plasticity has emerged in the context of schizophrenia (Stephan et al., 2009), neuropathic and phantom limb pain (Flor, 2008; Hirai et al., 2017), neurodegenerative disease (Milnerwood et al., 2006), epilepsy (Artinian et al., 2015), tinnitus (Shore et al., 2016), and posttraumatic stress (Deppermann et al., 2014). Instead, Brouwer and Carhart-Harris (2020) argue that psychedelic-induced transient states of hyper-plasticity, which they refer to as 'pivotal mental states' (PiMS), can lead to either adaptive or maladaptive change, depending on surrounding context and relational frame in which the PiMS occurs. This decidedly biopsychosocial perspective is grounded on the idea of experience-dependent plasticity (May, 2011) and compatible with an enactive view of neuroplasticity that supposes a diachronic circularity between (experiential) process and (neuronal) structure (Fuchs, 2020).

Oscillatory neural dynamics. Through irregular excitation of deep-layer pyramidal neurons, serotonergic psychedelics induce asynchronous glutamatergic postsynaptic potentials (Aghajanian & Marek, 1999) resulting in a temporal dissociation between cortical pyramidal cell firing and the active phase of local field potentials, a phenomenon known as spike-field decoherence (Celada et al., 2008). This neural desynchronization is believed to underlie the profound reductions in oscillatory activity - particularly in the alpha frequency band - observed in animal (Celada et al., 2008; Tylš et al., 2023; Vejmola et al., 2021) and human studies of psychedelics using electroencephalography (EEG) (Murray et al., 2022; Riba et al., 2002; Schenberg et al., 2015; Timmermann et al., 2023) and magnetoencephalography (Muthukumaraswamy et al., 2013). Alpha oscillations have been associated with deep layer pyramidal neurons which constrain incoming sensory information, relevant for top-down predictive processing (Bastos et al., 2012), explaining their functional relevance in cognitive and attention processes (Klimesch, 2012), known to be impaired under psychedelics (Basedow et al., 2024). Their disruption is thus consistent with the REBUS model, which posits that psychedelics reduce the precision-weighting of high-level priors, thereby allowing for an increased influence of bottom-up sensory inputs (Carhart-Harris & Friston, 2019).

Observations of psychedelic-induced broadband neural desynchronization also informed the ‘entropic brain theory of consciousness’ (Carhart-Harris, 2018; Carhart-Harris et al., 2014), which links stochastic properties of brain activity to a linear conception of consciousness, suggesting “that the quality of any conscious state depends on the system’s entropy measured via key parameters of brain function” (Carhart-Harris et al., 2014). According to the entropic brain theory, psychedelics’ subjective effects are explained by increased unpredictability, i.e. entropy, of neural activity that is consistently observed following psychedelic use (Atasoy et al., 2017; Schartner et al., 2017; Tagliazucchi et al., 2014;

Timmermann et al., 2023; Viol et al., 2017). This view that has since been supported by several studies, showing correlations of Lempel-Ziv (Lz) complexity, a measure of pattern diversity, with subjective effects under psilocybin, ketamine (Schartner et al., 2017), and LSD (Mediano et al., 2024), as well as enduring changes in personality (Lebedev et al., 2016) and revised negative self-beliefs (Zeifman et al., 2025).

Explaining the context-dependence of psychedelic effects invoked by REBUS and PiMS, high-entropy states have been hypothesized to increase sensitivity to external perturbation (Carhart-Harris, 2018). Fascinatingly, in a study operationalizing external perturbation on four levels, having participants sit a) with closed eyes in silence, b) eyes closed with music listening, c) eyes open in silence, and finally, d) watching a video, Mediano et al. (2024) found evidence for an interaction effect between sensory stimulation and LSD administration on Lz complexity: While greater levels of sensory stimulation linearly increased Lz complexity, this effect was greater for placebo, than for LSD. In other words, sensory stimulation seemingly diminished or, at least, competed with the effect of LSD on Lz complexity. This demonstrates that psychedelics not only produce changes in subjective experience by enhancing neural signal complexity, but the content of subjective experience (manipulated here via levels of sensory stimulation) can also alter how psychedelics affect neural activity. It is difficult to imagine a better illustration of circular causality between subjective and neural psychedelic effects, as suggested by enactive interpretations of psychedelic effects presented here (Figure 1.1) or by Meling and Scheidegger (2023).

Brain functional and network connectivity alterations. As described above, the desynchronization of local oscillatory activity following psychedelic 5-HT2AR agonism leads to reductions of within-network integrity (Muthukumaraswamy et al., 2013). This effect has

also been replicated using functional magnetic resonance imaging (fMRI) during acute psychedelic effects (Siegel et al., 2024). Evidence of within-network disintegration is especially robust in networks that densely express 5-HT2AR, such as the visual network and DMN (Gattuso et al., 2022; Madsen et al., 2021; Mason et al., 2020; Müller et al., 2018; Palhano-Fontes et al., 2015). Additional studies have found the reduction of within-network integrity to be accompanied by functional desegregation of anticorrelated networks, i.e. greater connectivity between functionally and hierarchically segregated brain networks (Girn et al., 2022; Roseman et al., 2014; Siegel et al., 2024; Singleton et al., 2022; Vohryzek, Cabral, et al., 2024; Vohryzek, Kringelbach, et al., 2024). This effect, which has been found to correlate with the intensity of subjective psychedelic effects (Madsen et al., 2019; Timmermann et al., 2023). Findings of psychedelic-induced functional desegregation are reflected also in decreased brain modularity (Daws et al., 2022) and increased global functional connectivity (Petri et al., 2014; Preller et al., 2020; Tagliazucchi et al., 2016; Timmermann et al., 2023) under psychedelics.

Beyond the trend of global functional integration, region-specific effects of psychedelics have been largely inconsistent, which has led to the view that a complex systems perspective may be more suitable to account for the significant context-dependent, intra- and interindividual variability in psychedelic effects (Girn et al., 2023). Specifically, neuroimaging studies have revealed a greater repertoire of stable brain states under LSD and psilocybin (Atasoy et al., 2017; Lord et al., 2019; Tagliazucchi et al., 2014), which can be understood as an increase in the functional metastability of the brain, i.e. the capacity to shift between transiently stable states of coordinated brain activity. In this view, analyses of brain activity are informed by the temporally shifting and context-dependent processual nature of subjective experience, emphasising the reciprocal coupling between neurobiology, phenomenology, and environment.

Organismic and peripheral effects. On an organismic level, research interest has largely focused on the effects of psychedelics on markers of immune function (Nichols, 2022; Szabo, 2015). Immunomodulatory effects of psychedelics have been shown in animal models (Low et al., 2024), finding anti-inflammatory effects primarily in conditions of pre-existing inflammation. In humans, acute and persisting reductions in pro-inflammatory cytokines have been detected in one observational study (Mason et al., 2022). A pooled study of controlled psilocybin administration has found a post-acute (<1 week) but no persisting increase in one anti-inflammatory cytokine (DiRenzo et al., 2024) and another study of psilocybin in healthy participants detected no immunomodulatory effects (Burmester et al., 2023). The density of serotonin receptors in the gut has led some to speculate for a role of the gut-brain axis in psychedelic immunomodulation (Caspani et al., 2024; Kargbo, 2023; Kuypers, 2019), but this theory has so far found not gained any empirical support from human research.

Better validated are the effects of psychedelics on the autonomic nervous system (Li et al., 2025). Acute psychedelic use is known to elevate sympathetic nervous system activity (Gouzoulis-Mayfrank et al., 1999; Holze et al., 2022; Holze, Vizeli, et al., 2021; Holze et al., 2020; Strassman et al., 1994) and this effect has been found to correlate with reported subjective drug effects (Olbrich et al., 2021; Pasquini et al., 2024). A recent study applied a measure of entropy (i.e. stochastic unpredictability) to both neural activity and heart rate (HR) under psychedelics and found changes in HR entropy to be correlated with both brain entropy and aspects of the subjective experience (Rosas et al., 2023). While brain entropy was found to be the best predictor of simple and complex imagery and ego dissolution, HR entropy was superior at predicting positive mood, and mean HR was most predictive of overall intensity and emotional arousal. In another study, the coactivation of the sympathetic and parasympathetic nervous systems was significantly correlated with the subjective intensity of

insightfulness and spiritual experience, as well as long-term improvements in well-being (Bonnelle et al., 2024). Together, these findings demonstrate the value of an embodied view of cognition for understanding psychedelic drug action, recognizing the potential role of basic interoceptive self-experience by integrating neural, autonomic, and subjective processes.

Summary of biological processes. Research on the biological effects of psychedelics, from molecular to cellular, neural, and organismic processes, has been extremely prolific. Unifying theories such as REBUS provide conceptual frameworks that integrate observations from several of these levels, attempting to explain the emergence of subjective drug effects and enduring psychological change. Importantly, compelling initial findings such as those by Mediano et al. (2024), indicate reciprocal effects of environmental and subjective experience on psychedelic-induced brain dynamics. This suggests that the causal relationships between biological, psychological, and social system domains may not be sufficiently explained as linear. The following sections will proceed to summarize evidence of the psychological, and finally, psychosocial dimensions of psychedelic drug effects, aiming to further illustrate how an enactive and embedded view of human experience is best suited to understand the crucial importance of context in psychedelic drug action (Carhart-Harris, Roseman, et al., 2018; Meling & Scheidegger, 2023).

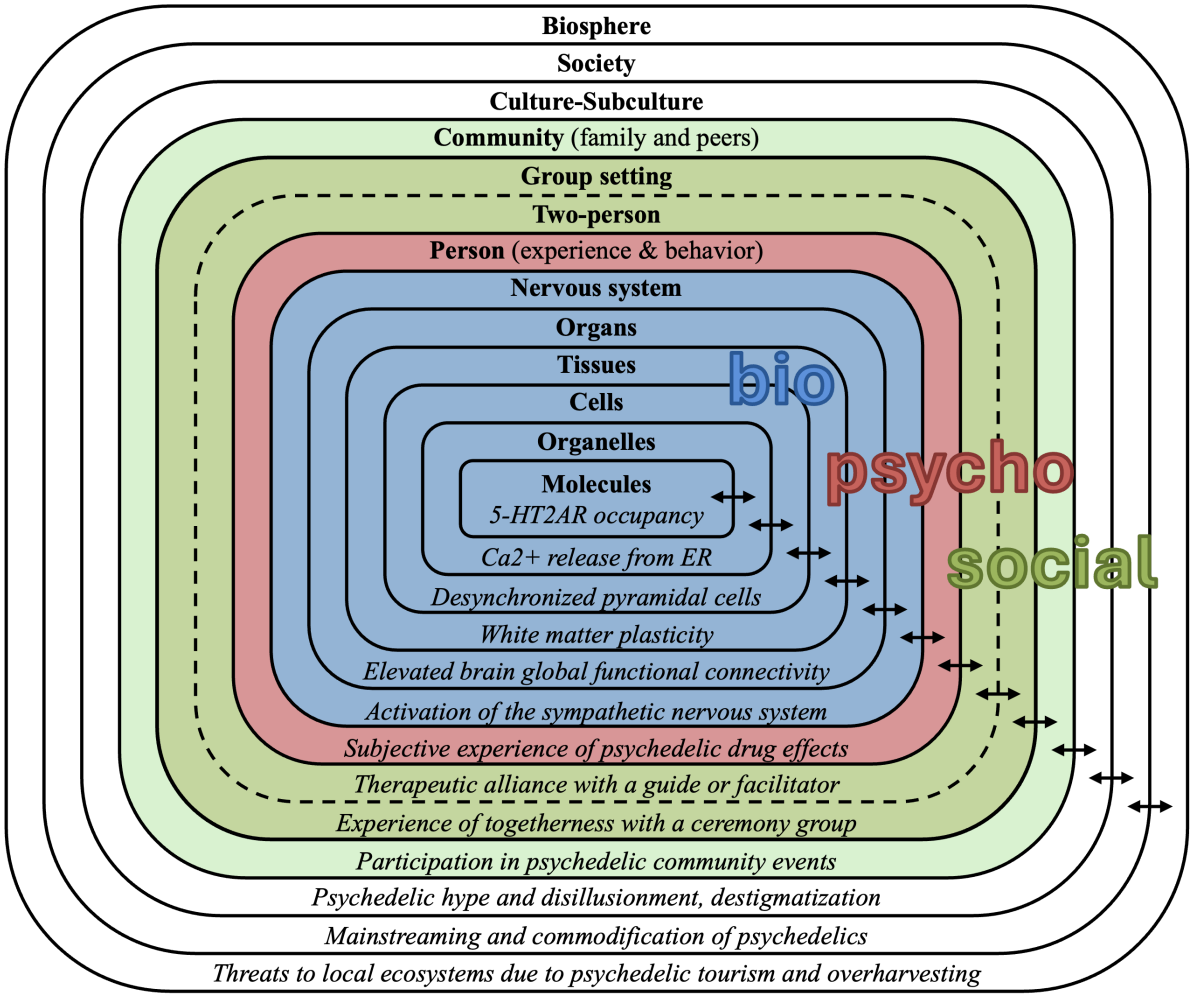


Figure 1.2 A Biopsychosocial Model of Psychedelic Effects. System levels are indicated in bold, operationalizable examples for each level in italics. All system levels are thought to stand in reciprocal dynamic relationship to each other, indicated by arrows. Not all potential system-level-interactions are indicated by arrows, as there may be direct effects from non-adjacent system levels. Adapted from Farre & Rapley (2017).
5-HT2AR: Serotonin 2A receptor; ER: Endoplasmic Reticulum; Ca: Calcium

1.3.2 Psychological Processes

Acute subjective effects. When ingested by humans, classic psychedelics such as psilocybin, can produce alterations to perception, thought, emotion, and sense of self, that are dose-dependent (Hasler et al., 2004). One, or perhaps *the* characteristic quality underpinning these subjective effects is their extreme affective and qualitative variability, recognized already in their eponymous communication (i.e., “to fathom hell or go angelic”, Bisbee et al., 2018) or in the conception of psychedelic drugs as ‘unspecific amplifiers’ (Grof, 1973).

Perceptual and cognitive effects. On a perceptual level, serotonergic psychedelics characteristically elicit open and closed eye visual hallucinations, including, but not limited to, elementary and complex geometric patterns, enhanced colours, object distortions and morphing, trail and tracer effects, and visual synaesthesia (Aqil & Roseman, 2023; Roseman et al., 2016). The breadth and depth of psychedelic-induced visual alterations are so great that psychedelics are sometimes equated with hallucinogens (Johnson et al., 2008; Nichols, 2004), although the latter group of drugs also includes non-serotonergic substances, such as dissociatives and anticholinergics (Garcia-Romeu et al., 2016). Other perceptual effects can include changes to auditory and tactile perception, multisensory hypersensitivity, non-visual forms of synaesthesia, changes in intero- and proprioception, including changes to the body schema, agentic hallucinations (perception of agency), altered sense of time, and many rarer and idiosyncratic effects (Masters & Houston, 2000; Shanon, 2002).

Empirically studied acute alterations to thought and attention include robustly impaired executive function and attentional performance across a variety of cognitive tasks (for a recent review, see Basedow et al., 2024), with some evidence also pointing to memory impairments (Healy, 2021), although recent findings suggest that certain aspects of episodic memory may be enhanced under psychedelics (Doss et al., 2024). Interestingly, while impairments in executive function explain how psychedelics may disrupt convergent thinking (relevant for narrow problem-solving), a number of studies have found enhanced divergent, ‘out-of-the-box’ creative thinking while acutely on psychedelics (Kuypers et al., 2016; Prochazkova et al., 2018; Wießner et al., 2022), although this effect seems to be somewhat inconsistent and may depend on the type of test used (Costa, 2023; Mason et al., 2021). Interestingly, Mason et al. (2021) found acute psilocybin-induced feelings of spontaneous creative insight to be predicted by decreased within-network DMN integrity in the brain, in line with recent findings of acute

psychological insight being correlated with Lz complexity in the parietal cortex (Lyons et al., 2024), both findings lending credence to the role of brain entropy and disruption of transmodal high-level brain areas, as predicted by REBUS.

Mystical-type and emotional effects. Perhaps the most intensely studied domain of acute subjective psychedelic effects in humans lies in their ability to profoundly alter one's sense of self, to the extent that perceived self-world boundaries can be entirely dissolved, leading to peak, or 'mystical-type' experiences (Barrett et al., 2015; Garcia-Romeu et al., 2014; Griffiths et al., 2006; MacLean et al., 2011; Pahnke, 1969),. This effect is closely correlated to the modernized concept of ego-dissolution (Lebedev et al., 2015; Millière, 2017; Nour et al., 2016), which has been evoked to explain the phenomenological proximity of psychedelic and certain non-pharmacologically induced altered states of consciousness, such as near-death experiences (Martial et al., 2021), spontaneous mystical experiences (Griffiths et al., 2019), and types of meditation (Holas & Kamińska, 2023; Millière, 2017). More than any other aspect of subjective psychedelic effects, mystical-type experiences have repeatedly and consistently been found to predict psychedelics' enduring psychological effects, including therapeutic benefits (Ko et al., 2022). Across 34 controlled studies, Romeo et al. (2025) found a modest but highly significant average correlation of r=.33 between relevant measures of psychedelic effects and long-term symptom improvements in the respective target psychopathology. Similarly, reviewing 44 controlled and naturalistic studies, Kangaslampi (2023) noted statistically significant predictive effects of mystical-type experiences on target outcomes for 57 out of 75 reported associations.

As suggested by Osmond's name-giving communication (Bisbee et al., 2018), the emotional effects of psychedelics can be both intensely negative and intensely positive, sometimes within the same experience. The above-described impairments of cognitive

function, thought disturbances, and alterations to self-experience can co-occur with intensely anxiogenic responses (Barrett et al., 2016; Carbonaro et al., 2016; Guthrie, 2021; Johnstad, 2021), but also peak experiences characterized by strong positive affect and even bliss (Barrett et al., 2015; Goldy et al., 2024; Hood Jr, 1975; MacLean et al., 2012; Pahnke, 1969). The directionality of affective responses to psychedelics has been linked to preexisting personality traits such openness to experience, acceptance, extraversion, and neuroticism (Aday et al., 2021; Ko et al., 2023; Smigielski et al., 2019; Vizeli et al., 2024), and, more strongly, to the psychological state immediately prior to dosing, including state anxiety, preoccupation, emotional excitability, feelings of preparedness and readiness to surrender (Aday et al., 2021; Haijen et al., 2018; Russ et al., 2019a; Russ et al., 2019b; Simonsson et al., 2023; Studerus et al., 2012). The strongest personality trait predictor of subjective psychedelic effects has consistently been identified as trait absorption, enhancing positive effects, but also subjective drug intensity in other domains (Aday et al., 2021; Haijen et al., 2018; Russ et al., 2019a; Smigielski et al., 2019; Studerus et al., 2012).

Highly relevant to the emotive, embodied quality of acute psychedelic effects, however less researched empirically, is their purported ability to attenuate ego-defences (Buchborn et al., 2023), which is thought to allow for the emergence of suppressed emotionally salient material, opening an opportunity for emotional processing and potentially, release (Roseman et al., 2019). Indeed, several recent studies, including the one presented in Chapter 4 below, have found experiences of emotional release or ‘breakthrough’ (Roseman et al., 2019) to be equal or superior at predicting therapeutic outcomes compared to mystical-type experiences (Murphy et al., 2022; Nygart et al., 2022). Music, known to be effective for evoking autobiographical memories and emotions (Janata, 2009; Trost et al., 2011), is thought to play an important guiding role in this process (Kaelen et al., 2018; MacLeod et al., 2025;

O'Callaghan et al., 2020). Interestingly, while psychedelics have been found to enhance subjective emotional responses to music (Bonny & Pahnke, 1972; Kaelen et al., 2015; Shukuroglou et al., 2023), the addition of music has conversely also been found to alter psychedelic-induced changes to functional brain activity (Kaelen et al., 2016; Shukuroglou et al., 2023; Wall et al., 2023) – another example of reciprocal causal dynamics between brain states and subjective experiences, the latter being altered in this case through music as a sensory stimulus from the environment.

In summary, the characterization of psychedelics as non-specific amplifiers (Grof, 1973) of both intrapsychic and external stimuli seems well-suited to explain the breadth of their subjective effects. Findings reviewed here and in the sections above showing phenomenological correlates of psychedelic-induced brain activity, combined with evidence of interaction effects between psychedelic administration and environmental conditions, underline the value of pluralistic multilevel causal frameworks, such as the BPSM, according to which psychedelic mind-brain states are best understood as co-emergent from reciprocal brain-person-environment feedback loops, as suggested by an enactive biopsychosocial perspective on psychedelic effects (Figs. 1.1, 1.2).

1.3.3 Social Processes

Compared to the biological and psychological processes involved in psychedelic drug action, significantly less empirical research has examined the social and relational dimensions of psychedelic use. This gap is striking, given the inherently psychosocial structure of psychedelic therapy and the socially constructive role of psychedelics in cultures that have developed ritualized consumption practices (Andritzky, 1989; De Rios, 1984; Rodríguez Arce & Winkelman, 2021; M. J. Winkelman, 2010). The following sections will review research on

the social determinants and effects of psychedelic use, including their impact on social cognition, the role of dyadic relationships such as the therapeutic bond, potential intersubjective dynamics in group-based psychedelic use, and broader sociocultural influences on psychedelic effects.

Effects on social cognition. Social cognition refers to the processes underlying perception, interpretation, and response to social stimuli, including empathy, prosocial behaviour, and social emotion recognition, some of which have been found to be modulated by psychedelic substances (Preller & Vollenweider, 2019). Among the most replicated results is the acute and post-acute enhancement of emotional empathy following psychedelic use (for a review and meta-analysis, see Blatchford et al., 2021; Olami & Peled-Avron, 2024), typically assessed via ratings of concern (explicit emotional empathy) and arousal (implicit emotional empathy) in response to emotional faces (Dziobek et al., 2008). In a controlled study in 21 healthy participants, Preller et al. (2015) found acutely enhanced emotional but not cognitive empathy, the latter being the ability to correctly identify emotion in facial expressions. In the same study, a task simulating social ostracism showed reduced neural responses in the anterior cingulate cortex in response to social exclusion, indicating a positivity-bias in processing of social experiences. This is in line with other studies showing impaired recognition of negative emotional states in faces under LSD (Dolder et al., 2016) and psilocybin, which could be blocked by administration of the 5-HT2AR antagonist ketanserin (Kometer et al., 2012). The mediating role of the 5-HT2AR for acute prosocial psychedelic effects was partially confirmed in another recent study demonstrating increased emotional empathy and increased levels of circulating oxytocin after administration of LSD, although in this case only the latter was reduced by ketanserin (Holze, Avedisian, et al., 2021). Dolder et al. (2016) and Pokorny et al.

(2017) similarly found acutely enhanced prosociality and emotional empathy under LSD and psilocybin, respectively.

Beyond the acute psychedelic state, the finding of increased emotional empathy post-psychedelic was recently replicated up to two weeks after psilocybin administration in a clinical sample of patients suffering from major depression (Jungwirth et al., 2024). Similarly, others have observed enhanced emotional empathy after participation in a naturalistic group setting using psilocybin (Mason et al., 2019) and increased cognitive and implicit emotional empathy after ayahuasca (Kiraga et al., 2021; Uthaug et al., 2021) for up to a week. A retrospective online survey study on the relationship of acute psychedelic effects, empathy, and trait narcissism, recently indicated that specifically experiences of awe, but not ego-dissolution, may increase empathetic drive and feelings of connectedness, which in turn lowered narcissistic personality traits (van Mulukom et al., 2020). While prospective studies will be necessary to confirm the role of subjective psychedelic effects on changes in social cognition, this is in line with prior research linking the self-transcendent nature of awe to a diminished sense of self and enhanced prosocial behaviour (Perlin & Li, 2020; Piff et al., 2015). Although not yet empirically demonstrated in the context of psychedelics, the robust changes in emotional empathy and social positivity biases are likely to enhance psychological well-being and affect, which in turn may foster prosocial behaviour (Forstmann & Sagioglou, 2025). This dynamic could create a self-reinforcing cycle of reciprocal interpersonal and emotional benefits driving sustained therapeutic outcomes (Bhatt & Weissman, 2024) and exemplifying a personal-interpersonal feedback loop within the psychosocial level of the enactive BPSM (Fig 1.1).

Dyadic interpersonal processes. The therapeutic alliance—a collaborative partnership between therapist and patient—has long been recognized as a critical factor in the success of psychotherapy. Meta-analyses encompassing up to 295 studies and 30,000 patients have demonstrated a robust association between the strength of the therapeutic alliance and positive psychotherapy outcomes (Flückiger et al., 2018; Horvath et al., 2011; Horvath & Symonds, 1991; Martin et al., 2000). This correlation underscores the importance of mutual trust, agreement on therapeutic goals, and collaboration on tasks within the therapeutic relationship.

In the context of psychedelic therapy, the significance of the therapeutic alliance may be even more pronounced, given the vulnerability and volatility of the psychedelically altered state of consciousness. Despite decades of emphasis on the importance of trust in such settings, however, there remains a surprising lack of empirical research examining this specific aspect (Kamilar-Britt et al., 2023). Thus far, only one study has replicated the findings presented in Chapter 3: Specifically, in a trial of psilocybin for major depression, higher alliance ratings at the final preparation time point were associated with higher mystical type experience and insightfulness scores, which in turn were predictive of depression outcomes at 4-weeks (Levin et al., 2024). Notably, this study also found an exceptionally strong direct correlation ($r = .85$) between pre-session alliance ratings and depression outcomes at four weeks, with a significant association ($r = -.61$) persisting even at the 12-month follow-up.

While further empirical studies on the therapeutic relationship within psychedelic therapy are much needed, some of the characteristics that may be predictive of positive therapeutic bonds in this context have been investigated in an online survey study (Thal et al., 2022), with respondents indicating that mutual trust, presence, compassion, and empathy, would be desirable characteristics in psychedelic care providers. The authors related these

findings to the concept of an "empathetic abiding presence," as discussed by Phelps (2017), which emphasises the therapist's role in providing a consistent, compassionate, and empathetic presence during psychedelic sessions.

Looking towards dyadic relationships outside the immediate context of psychedelic dosing sessions, a small number of qualitative and survey studies have begun exploring potential effects of psychedelic use on romantic partnerships. Combining pooled data from two large-scale prospective observational studies of naturalistic psychedelic use and a clinical trial comparing escitalopram and psilocybin for major depression, we recently reported improvements on several items assessing relationship satisfaction, communication, and aspects of sexual satisfaction and functioning post-psychedelic (Barba et al., 2024). In contrast, a majority of patients receiving the conventional antidepressant escitalopram reported no change or worsening of sexual functioning (Barba et al., 2024), a well-known side-effect of SSRIs. Our findings of improved sexual functioning and communication related to psychedelic use have since been supported by a qualitative interview study of four couples using microdoses of psilocybin, LSD, or MDMA during sexual encounters, reporting themes of increased sexual confidence, mindfulness, and exploration, combined with reduced anxiety (Jacobs et al., 2024). In another interview study of couples naturalistically using psychedelics together in non-sexual settings, Neubert et al. (2024) correspondingly emphasised themes of interactional intimacy, expressed in shared experiences of bliss, but also in preparation activities, and the mitigation of anxiety through co-regulation. While extremely preliminary, these findings indicate firstly how naturalistic and even clinically supervised individual psychedelic experiences can impact interpersonal relationships outside the immediate context of psychedelic use (Barba et al., 2024), and secondly, how interpersonal (romantic) relationships can conversely impact the progression of naturalistic psychedelic experiences. The use of psychedelics as a shared activity

will also be the focus of the following section, examining research on group-level psychosocial dynamics in psychedelic-assisted group therapy and naturalistic use in group settings.

Group-related intersubjective processes. Although no representative prevalence data on psychedelic use settings appears to have been published, it is likely that most non-clinical psychedelic use takes place not in solo, but group settings, with two or more people taking a psychedelic together. In a self-selected sample of psychedelic users recruited through online fora, only about 10% (59/578) reported a history of exclusive solo use experiences, with almost triple the amount of participants (28%) having only ever used psychedelics in group settings, and a majority (62%) having experience in both (Byrne et al., 2023). This is reflective of the collective nature of many events in which psychedelics are commonly consumed, such as raves (Kyriakopoulos, 2021; Milshteyn & Bensimon, 2023), festivals (Forstmann et al., 2020), religious ceremonies (Hartogsohn, 2021; Labate & MacRae, 2016), or at psychedelic retreats (Rucker & Young, 2021; Winkelman, 2005). Nevertheless, while their intraindividual processes, including biological, psychological, and social cognitive effects have been studied extensively, there exists little to no quantitative research on intersubjective processes that could be involved in collective psychedelic use. A possible explanation for this may be the relative absence of group therapeutic approaches from clinical psychedelic research, although considering the above mentioned scarcity of research even on dyadic processes (Kamilar-Britt et al., 2023), the neglect of social processes within psychedelic research appears to be more generalized.

Lines of research that could inform an inquiry into intersubjective psychedelic effects include the social psychology of collective events, especially those involving altered states of consciousness (Rose, 2025), and group psychotherapy research. For example, Ponomarenko et

al. (2023) have begun identifying concepts validated in group psychotherapy, such as group cohesiveness, interpersonal learning, or catharsis, within psychedelic-assisted group psychotherapy, which has been practiced legally in Switzerland under the compassionate use program (Gasser, 2022; Oehen & Gasser, 2022). The Swiss format combines long-term individual psychotherapy with group dosing sessions using LSD and/or MDMA, originally informed by the school of psycholytic psychotherapy (Leuner, 1971). Oehen and Gasser (2022) report results of 22 group sessions over a period of more than 5 years, with a total of 50 patients, who participated in a variable number of group medication sessions, while undergoing individual psychotherapy before and after sessions. Among the 50 patients, who suffered primarily from trauma-related disorders, anxiety and depression, only one deteriorated, while 33 out of 50 (66%) showed clinical improvement according to the authors' clinical judgement. A study drawing on similar psychedelic psychotherapy groups compared acute subjective drug effects to those in solo experiences in clinical trials and found no significant differences (Schmid et al., 2021). While group therapy may require additional training, its qualitatively reported advantages include increased connectedness, the opportunity to practice prosociality, to enhance interpersonal learning and to directly apply newly acquired insights, similar to non-psychedelic group psychotherapy (Ponomarenko et al., 2023)

Introducing a different approach to group-based psychedelic interventions, Anderson et al. (2020) conducted a clinical trial involving solo psilocybin administration sessions that were embedded in up to 10 group psychotherapy visits. The authors reported significant reductions in demoralization, PTSD symptoms and complicated grief in the sample of AIDS survivors that was recruited for the study (Anderson et al., 2020). Qualitative interviews with this sample showed that the group format was felt to enhance the effectiveness of trauma processing by reinforcing social cohesion, safety, trust, and belonging (Agin-Liebes et al.,

2021). In another modern psychedelic group psychotherapy trial, rapid and sustained improvements in cancer related depression were reported following a small group-psilocybin session bookended by three group preparation and three group integration sessions (Lewis, Garland, et al., 2023). During a follow-up surveys in this group, 100% (10/10) participants indicated that the group format worked well to maximize their therapeutic response, with 9 out of 10 agreeing strongly with this statement (Lewis, Byrne, et al., 2023). Together, these outcomes strongly suggest that more research is warranted on the potential of group-based psychedelic interventions (Trope et al., 2019), especially considering that they could significant improve accessibility by reducing the cost of treatment (Marseille et al., 2023).

Acknowledging the safety benefits of highly controlled clinical and laboratory environments, the practice of psychedelic-assisted (group) psychotherapy bears a number of similarities to naturalistic use in guided ceremonial settings implemented by psychedelic retreats, which have rapidly grown in popularity during recent years (Glynos et al., 2024; Thiessen et al., 2018). Usually, naturalistic psychedelic ceremonies are conducted by one or more individuals who have acquired this skill through formal training or experience in the care for others during psychedelic experiences. These practitioners (e.g., ‘shamans’, ‘ayahuasceros’ or ‘curanderos’ in the context of ayahuasca ceremonies; ‘facilitators’, ‘sitters’ or ‘guides’ in Western settings) would often facilitate preparatory and integration before and after dosing, similar to psychedelic therapy protocols (Chisamore et al., 2024; Harris & Gurel, 2012). Additionally, akin to clinical psychedelic spaces, dosing environments would be aesthetically enriched making use of decorative or ritual objects, special lighting, comfortable seats or bedding. During sessions, facilitators intend to provide emotional support to participants, sometimes through direct interaction, including supportive touch, and usually indirectly through the medium of music. While modern psilocybin retreats often use recorded playlists

similar to those used in clinical trials, live music, including Rattling, drumming, singing and whistling, sometimes including the group's active participation, are typical elements in Meso and South American settings of mescaline cacti and ayahuasca use (De Rios & Katz, 1975).

Converging lines of research are indicating that the naturalistic group use of psychedelics can lead to long-lasting psychological benefits. Ceremony experiences have been reported as positive, valuable, and in many cases associated with health improvements by both naïve and regular participants (Barbosa et al., 2009; Loizaga-Velder & Verres, 2014). Furthermore, observational studies have found increased well-being (Bouso et al., 2012; Kiraga et al., 2021; Uthaug et al., 2018), reduced depression (Palladino, 2009; Sobiecki, 2013), anxiety (Kiraga et al., 2022; Perkins et al., 2022; Ruffell et al., 2021; Uthaug et al., 2021), suicidality (Zeifman et al., 2020) and reduced abuse of alcohol and other addictive drugs in regular ceremony participants (Doering-Silveira et al., 2005). Importantly, qualitative interviews with facilitators of psychedelic retreats have pointed out that community is seen as central for their therapeutic effects (Dorsen et al., 2025), in line with the 'social cure' model recently proposed by Newson et al. (2024), who speculate that group experiences may promote well-being through changes in social identity mediated by experiences of support, belonging and trust.

On the intersection of interpersonal and sociocultural processes lies the purported ability of psychedelics to be tools not just for belief-relaxation (Carhart-Harris & Friston, 2019), but also belief transmission. This idea is supported by experimental research showing that LSD can not only enhance suggestibility (Carhart-Harris et al., 2015), but also shift participants' beliefs depending on presented social norms: Duerler et al. (2020) found that participants' subjective ratings of the aesthetic quality of images moved closer to a presented group norm while under the acute effect of LSD, compared to placebo. Interestingly, however,

this relationship was inverted when the degree of conflict between the participants' initial opinion and the presented norm was high, suggesting that psychedelics may render beliefs more malleable to outside influence only if the imposed external beliefs are not too different from one's own. While the ecological validity of such tasks is questionable, we found enduring shifts in metaphysical beliefs in participants attending psychedelic group ceremonies, which were mediated by the intersubjective experience of emotional synchrony during drug sessions (Timmermann et al., 2021). This suggests that intersubjective experiences in group settings may indeed mediate the alterations to existing belief structures and systems, softened by the influence of serotonergic psychedelics.

Similarly, based on detailed ethnographic case-studies, Dupuis (2021, 2022) described how the content of psychedelic experiences could not only be shaped by surrounding cultural priors, but how psychedelics could inadvertently or intentionally function as tools for belief transmission in social settings. This could also explain why prior studies have observed directional changes in political beliefs towards more liberal and anti-authoritarian positions following psychedelic use in controlled solo settings (Lyons & Carhart-Harris, 2018). Even though these studies did not involve any explicit political education, the context of the research, and the researchers themselves could have transmitted implicitly held assumptions, e.g., regarding the need for more liberal or scientifically guided drug policies. The notion that at least some psychedelic-induced changes in beliefs may be a consequence of the social environment, rather than substance-intrinsic, finds additional support in contrary examples of authoritarian or otherwise illiberal movements utilizing psychedelics (Pace & Devenot, 2021). Together, these findings highlight the ethical challenge of navigating potential epistemic vulnerabilities among participants in both naturalistic and clinical settings of psychedelic use (Langlitz et al., 2021; Pedersen & Steglich-Petersen, 2024; Timmermann et al., 2022). An

elevated responsibility lies with the curators of psychedelic spaces to remain critically aware of the interplay of psychological, social, and cultural factors that may shape participants' idiosyncratic experiences and interpretations. The need for culturally informed practices in psychedelic research will be further clarified in the next section, reviewing evidence of sociocultural processes influencing psychedelic effects.

Sociocultural processes. Social categories, such as race, ethnicity, and religion, fundamentally structure both interpersonal relationships and the broader environments in which psychedelic experiences unfold. These categories shape subjective and intersubjective experiences in ways that extend beyond individual psychology, embedding psychedelic effects within wider social and cultural contexts (Blevins, 2023). Neitzke-Spruill (2019) has argued that race should be explicitly considered as a relevant aspect of set, emphasising how racialized lived experiences and social positioning may influence the phenomenology of psychedelic states. Yet, despite increasing awareness of these issues, psychedelic research remains disproportionately centred on white, Western populations, raising concerns regarding the generalizability of existing findings.

The lack of diversity in psychedelic research is not merely a methodological oversight but may have direct implications for the efficacy and applicability of psychedelic-assisted interventions across different populations. For instance, studies using large-scale nationally representative datasets suggest that the positive mental health outcomes associated with lifetime psychedelic use, such as lower rates of distress, suicidality (Jones & Nock, 2022) major depressive episodes (Jones, 2023), hypertension (Jones et al., 2024) - and even lowered odds of crime arrests (Jones et al., 2023) - are significantly diminished or absent in racial and ethnic minority groups. Similarly, Viña and Stephens found that Black individuals who use

psychedelics are more likely to face policing and legal consequences, and that they do not experience the same health benefits as white users (Vina, 2024; Viña & Stephens, 2023). These findings underscore the role of structural inequities in moderating both the accessibility and outcomes of psychedelic use, questioning the universal applicability of psychedelic research findings and therapeutic models.

Conversely, culturally informed psychedelic settings may provide meaningful benefits for people of colour and other historically marginalized groups. For example, a recent observational study found self-reported improvements of symptoms from racial trauma in a self-selected sample of north American people of colour (Williams et al., 2021). Additionally, we recently reported reductions of depression and trauma-related symptoms following participation in an ayahuasca retreat designed for Middle Eastern and North African immigrants and refugees (Lowe et al., 2024). Noteworthy in this context are also Roseman et al.'s studies on relational dynamics in groups of Israeli and Palestinians co-participating in ayahuasca ceremonies (Roseman & Karkabi, 2021; Roseman et al., 2021). Their detailed qualitative accounts offer narratives of interpersonal connection in face of difference in identity, an important contrast to universalist themes prevalent in many (ethnically homogenous) psychedelic and related new-age communities.

Despite the historical ties between psychedelics and spiritual traditions (Strassman, 2018), little research has examined how religious affiliation and underlying beliefs shape psychedelic effects. However, a recent study by Viña (2024) analysing a nationally representative dataset offers intriguing preliminary insights: Among individuals with weak religious beliefs, lifetime psychedelic use was found to be protective against distress, pointing to a possible compensatory role of psychedelics in contexts of low religious salience. The study

also revealed a three-way interaction between psychedelic use, religious salience, and religious service attendance, highlighting the importance of social integration. The protective effect of psychedelic use on distress was present in individuals with low religious salience who did not regularly attend religious services, but increased distress was observed among non-attenders with high religious salience, possibly reflecting an unmet need for religious or spiritual engagement. This pattern was reversed in individuals with regular attendance: Regular attenders with salient religious beliefs reported less distress if they had used a psychedelic, while psychedelic use was associated with increased distress when religious salience was low but attendance high. In summary, this suggests that psychedelics may amplify the influence of existing identity congruence or dissonance, enhancing well-being when belief and practice are aligned, but exacerbating distress when they are misaligned.

Beyond the influence of individual religious, ethnic, or racial identities on the outcomes of psychedelic use, collective societal values and expectations have been hypothesised to impact how psychedelic experiences are interpreted and integrated into personal narratives since the early wave of LSD research. Becker (1967) proposed that LSD-induced psychoses might, in part, be a product of sociocultural misunderstandings, where individuals lacking frameworks to interpret their altered states may default to psychiatric pathologization. Historical media representations of psychedelics may have reinforced such dynamics. For example, Bunce (1979) found that reports of “bad trips” peaked during periods of intensified media dramatization of psychedelic risks in the 1960s and 1970s, suggesting that fear-based cultural narratives may influence the likelihood and severity of challenging experiences. In contrast, contemporary portrayals of psychedelics tend to emphasise their therapeutic potential, creating strong cultural expectations of personal transformation and mental health improvements. Dupuis & Veissière (2022) argue that psychedelics in a therapeutic context may

thus function as "super-placebos", amplifying the effect of being in an interaction that the participant believes will be therapeutic - which could be influenced by opinions in their immediate community, as much as media reports. This super-placebo effect could activate biological and psychological mechanisms that may ultimately contribute to actual symptom improvement, reflective of an interaction between pharmacological, psychological, and social levels of the BPSM. However, attention has also been called to the risk involved in positive expectations: Positive publication biases in research, multiplied with biases in news media reporting on psychedelics, are likely to produce unrealistically optimistic hopes and expectations regarding their potential medical and societal benefits (Meling et al., 2024; Yaden et al., 2022).

The interplay between scientific research, media representation, and public interest has likely contributed to the recent substantial increase in psychedelic use, particularly for self-medication purposes (Bornemann et al., 2021; Mason & Kuypers, 2018; Matzopoulos et al., 2022). Concurrently, large-scale surveys indicate a decrease in the perceived risks of psychedelics (Barnett et al., 2023), aligning with an explosive rise in psychedelic consumption prevalence, doubling on average every 3-4 years (see Figure 1.3, Killion et al., 2021; Matzopoulos et al., 2022; Yockey & King, 2021; Yockey et al., 2020). These patterns highlight a recursive feedback loop: the number of scientific publications on psychedelics increases (Hadar et al., 2023), influencing public perception and media coverage, which in turn fuels further research interest and funding, and ultimately, wider adoption of psychedelics, both publicly, and increasingly also institutionally.

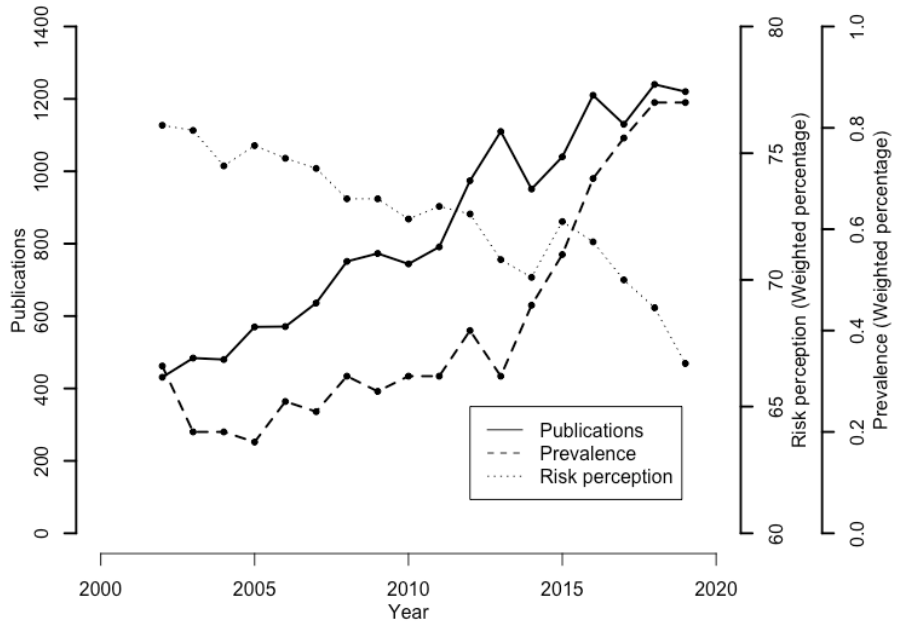


Figure 1.3 Trends in LSD Use Prevalence, Risk Perception, and Scientific Publications. Data from the US National Survey on Drug use and Health (NSDUH) were plotted on the right-hand y-axis; Trends in publications are based on a PubMED search.

This complex web of interdependencies - between drugs, their subjective effects, researchers, media narratives, and the public - exemplifies the outer layers of the multilevel, reciprocal processes described by enactive interpretations of the BPSM (Figure 1.2). Psychedelics do not exist in a vacuum; their effects emerge through dynamic interactions between individual neurobiology, psychology, and the social and cultural environment. Recognizing this interconnectedness is essential for the responsible development of psychedelic therapies and the ethical navigation of their growing societal impact. In acknowledging this reflexivity, the present body of research hopes to draw attention to the central role of human relationships in psychedelic practice—social processes often overshadowed by the biomedical linearity of the 'techno-medical' environment (Gaskin, 2010; Roseman, 2019a), within which we are momentarily acting as collective midwives to the emergence of psychedelics into medical practice.

1.4 Research Objectives

The main objective of this thesis was to investigate the psychosocial dimensions of psychedelic drug effects, with a particular focus on the role of interpersonal and social contexts in shaping both acute experiences and long-term outcomes. While psychosocial support is widely recognized as an essential element of psychedelic therapy, its precise mechanisms of action and therapeutic significance remain underexplored. Despite extensive research on the subjective effects of psychedelics, and their deep-rooted communal functions, little attention has been given to their intersubjective effects, i.e. relational dynamics within collective psychedelic experiences. Given the potential advantages of group-based psychedelic use, understanding their effects beyond the individual level is critical for both clinical applications and broader cultural considerations. Another key question addressed in this thesis is whether the psychosocially mediated effects of psychedelics are inherently tied to the pharmacological action of the drug or whether similar processes can emerge in non-substance-supported contexts. If psychedelics act as amplifiers of social and psychological processes, can comparable experiences be facilitated through structured, immersive, and interpersonally engaging interventions?

To explore these overarching questions, this thesis pursued three primary research aims:

Chapter 3 – Study 1: To examine the role of therapeutic alliance in shaping psychedelic experiences and their therapeutic potential in a clinical setting.

Chapter 4 – Study 2: To investigate the intersubjective and group-level processes in collective naturalistic settings of psychedelic use.

Chapter 5 – Study 3: To explore the therapeutic potential of non-pharmacologically mediated psychedelic-like experiences in a group virtual reality setting.

Chapter 2: General Methods

This chapter introduces some of the basic methodology used across the studies presented in this thesis. This includes firstly an overview of psychometric tools employed to assess the acute subjective effects of psychedelics. Additionally, the chapter outlines the use of factor and path analysis as statistical approaches utilized in this research. Detailed descriptions of the specific study designs, measures, and analyses are presented in the corresponding chapters for each individual study.

2.1 Measurement of Acute Subjective Psychedelic Effects

Historically, a variety of self-report questionnaires have been used to assess the acute effects of psychedelic drugs (Beecher, 1959). Among the earliest examples, Abramson (1955) used 47 questions rated on a 5-point scale (from + to +++++), which focussed primarily on autonomous bodily responses (e.g., sweating palms, dry mouth, need to urinate), but also included items assessing alterations to vision and feelings of anxiety. By administering this questionnaire at hourly intervals following three different LSD dose levels, Abramson et al. were for a first time able to visualize dose-response-time curves for LSD and statistically test hypotheses, finding for example a lack of a correlation between subjective effects and participants' bodyweights (Abramson et al., 1955). A modified version of this questionnaire split into three domains (physiological, perceptual, cognitive effects) was used in a study by Jarvik, Abramson, and Hirsch (1955) comparing subjective effects of different drugs within-subjects. Five participants were dosed on seven consecutive days with LSD, methamphetamine, alcohol, scopolamine, BOL-148 (the partial 2A agonist 2-Bromo-LSD), D-Lysergic acid ethylamide (LAE-32, an ergine derivative), ergometrine, or a placebo, reporting the greatest number, intensity, and variety of responses under LSD.

Using an alternative approach to questionnaire construction, Haertzen's (1963) Addiction Research Center Inventory (ARCI) was generated by having volunteers complete 200 open-ended sentences (e.g., "I am very…"), while under the effects of morphine, LSD, d,l-amphetamine, pentobarbital, chlorpromazine, or a synthetic cannabinoid. The resulting 3300 distinct sentences were then reduced to a final pool of 550 binary items meant to comprehensively distinguish between subjective drug effects. While the response burden involved in questionnaires of this length rendered the ARCI's original version mostly obsolete, Haertzen's work stands out due to its pioneering effort to apply factor analytic methods to this scale using early computer technology (Haertzen, 1965) and short forms remain in use in modern psychedelic trials (Griffiths et al., 2006). Newer measures of subjective psychedelic effects with a phenomenologically broad approach include the Altered States of Consciousness rating scale (ASC, Dittrich et al., 2010; Studerus et al., 2010) and the Hallucinogenic Rating Scale (HRS) (Strassman et al., 1994), which remain among the most widely used scales in psychedelic research (Herrmann et al., 2023).

The first content domain-specific measure assessing specific psychedelic effects emerged with Walter Pahnke's (1969) now-iconic "Good Friday Experiment", during which psilocybin was administered to divinity students during religious service in Boston University's Marsh Chapel. Building on William James' (1902) seminal work on religious experience and Walter Stace's (1960) typology of mystical states, Pahnke and Richards (Pahnke, 1966, 1969; Pahnke & Richards, 1966) developed a set of items seeking to assess the presence and intensity of six key features of mystical experience proposed by Stace: unity, transcendence of time and space, noetic quality, sacredness, positive mood, and ineffability/paradoxicality. The resulting Mystical Experience Questionnaire (MEQ) became the first structured tool for quantifying such subjective phenomena even though it was

psychometrically validated only much more recently (Barrett et al., 2015; MacLean et al., 2012), resulting in the MEQ30. This shortened 30-item version reduced the original six-factor structure to four latent factors: mystical (encompassing unity, noetic quality, and sacredness), positive mood, transcendence of time and space, and ineffability. The MEQ30 remains the most widely used measure of psychedelic-occasioned mystical-type experiences in current research, with recent updates including an abbreviated 4-item version (Strickland et al., 2024), an extended 40-item version re-adding dimensions pertaining to paradoxicality and connectedness (Stocker et al., 2024) and cross-cultural validation studies of translated versions in several languages (Andreas Aamodt Andersen et al., 2025; Davis et al., 2024; Fauvel et al., 2023; Hovmand et al., 2025; Wirsching et al., 2024; Yonezawa et al., 2024),

Surveying other self-response questionnaires used in modern psychedelic research, a recent review identified a total of 17 individual rating scales (Hovmand et al., 2024), including newer and less disseminated measures such as the 24-item Challenging Experiences Questionnaire (CEQ) (Barrett et al., 2016), comprising seven subscales meant to assess potentially difficult responses (fear, grief, physical distress, insanity, isolation, death, paranoia). The ego-dissolution Inventory (EDI) (Nour et al., 2016), consists of an ego dissolution (EDI-D) and an ego inflation (EDI-I) subscale with eight items each rated using a 0–100 visual analog scale (VAS) with the anchors “No, not more than usually” (0), and “Yes, entirely or completely” (100). The Emotional Breakthrough Inventory (EBI) (Roseman et al., 2019) uses a similar 0-100 VAS format across six items addressing the emergence, processing, and emotional release of difficult or traumatic memories during the psychedelic experience. Other recent instruments of note that are not used in the present research include the Psychological Insight Questionnaire (Davis, Barrett, So, et al., 2021) and Psychological Insight Scale, assessing acute and post-acute experiences of insight, respectively, which have been

shown to partially mediate the positive long-term effects of psychedelic experiences (Peill et al., 2022).

2.2 Statistical Methods

Across the studies presented below a range of standard parametric statistical techniques were used, including Spearman and Pearson correlations, paired and unpaired t-tests, Analysis of Variance (ANOVA), including repeated measures (RM) and multivariate ANOVA (MANOVA), factor analysis, and mixed linear regression models (MLM). These will be outlined individually in each Chapter.

Path analysis. The studies presented in Chapter 3 and Chapter 4 utilize path analyses, a special form of structural equation models (SEM) without latent variables. Path analysis was first developed by Sewall Wright in 1918 (Wright, 1918) and further described in 1934 (Wright, 1934) as a statistical approach allowing researchers to analyse and visualize ostensibly causal relationships between two or more variables by decomposing their correlation into direct and indirect effects based on some hypothesized underlying causal structure. This is achieved by simultaneously solving a system of prespecified multiple regression equations which can be visualized in form of a directed acyclic graph (DAG, Figure 2.1), where variables are represented as nodes and hypothesized causal paths as directed arrows. Each arrow corresponds to a regression weight (path coefficient) estimating the strength and direction of the effect from one variable to another, while accounting for other variables in the model.

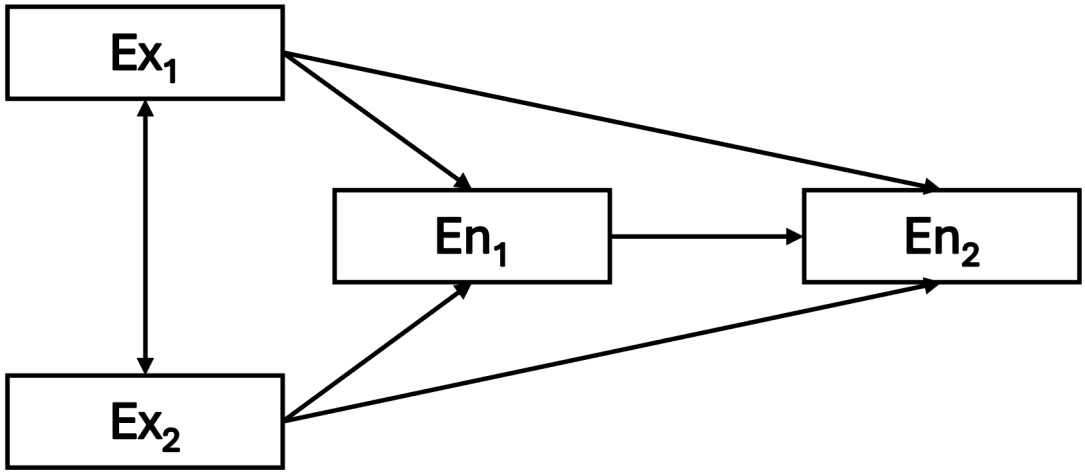


Figure 2.1 Example of a Directed Acyclic Graph (DAG). Unlike latent variable structural equation models, all variables are measured directly. Exogenous variables (Ex) only have outgoing arrows, as they are predictive variables not influenced by any other variable in the model, although they can covary with each other. Endogenous variables (En) can be either mediating or exclusively dependent variables, represented by incoming and optional outgoing arrows.

By specifying a particular theory-driven causal ordering among variables, path analysis enables the partitioning of total effects into direct effects (unmediated) and indirect effects (mediated through one or more intervening variables). Unlike simple regression, this multivariate framework allows researchers to formally test more complex, theory-driven models of influence, including mediational hypotheses. In doing so, path analysis offers a powerful tool for assessing the plausibility of causal mechanisms when experimental manipulation is unfeasible, assuming the underlying model structure is correctly specified and that statistical assumptions such as multivariate normality and linearity are met. This is especially useful in the case of prospective observational studies, such as those presented in Chapter 4, where hypothesized causal relationships between predictor and outcome variables cannot be manipulated experimentally, but satisfy the requirement of temporal precedence.

Path analysis, as a special case of SEM, relies on several statistical assumptions including multivariate normality, linearity of relationships, homoscedasticity, i.e. uncorrelated residuals, low multicollinearity, absence of measurement error, and appropriate treatment of

missing data. Wherever possible, diagnostic tests were conducted and included in Appendix B. Generally, these included: Marida's test for multivariate normality, Breusch-Pagan tests for homoscedasticity, Harvey-Collier tests for linearity, reporting of Variance Inflation Factor (VIF) for multicollinearity, and internal consistency (Cronbach's alpha) as an indicator of measurement error. Furthermore, maximum likelihood estimation with robust standard errors (MLR) was used for parameter estimation to mitigate effects of non-normality and heteroscedasticity which were present in most models. A full information maximum likelihood (FIML) approach to handle missing data was employed to maximize the use of collected data without need for multiple imputation. FIML has been shown to produce unbiased parameter estimates under the assumption that data are missing at random (MAR).

In terms of model fit evaluation, multiple fit indices were reported to assess how well the hypothesized path models accounted for the observed covariance structure. These included the Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA), Standardized Root Mean Square Residual (SRMR), and chi square to degrees of freedom ratio (χ^2/df). Generally, χ^2/df below 2, CFI values above .95, RMSEA and SRMR below .05 are taken to indicate good model fit (Hu & Bentler, 1999), unless otherwise specified.

The *lavaan* R package (version 0.6-12) was used to specify and estimate parameters. Custom syntax was used to define observed variables and their directed relationships, allowing for both direct and interaction effects. Interaction terms were computed prior to model entry and were mean-centred to reduce multicollinearity. Additional model diagnostics, including examination of modification indices and residual covariance matrices, were conducted when necessary to assess potential areas of misfit.

Finally, standard errors were computed using the sandwich estimator to ensure robustness, and bootstrapped confidence intervals were reported for indirect effects in mediation models when relevant. All modelling steps, data preparation procedures, and assumption checks were conducted using a fully reproducible R workflow, using RStudio versions 1.2 to 4.2.2.

2.3 Study Approvals

All studies were approved by Imperial College London's Joint Research and Compliance Office (JRCO) and were conducted in accordance with the revised declaration of Helsinki (2013), the International Committee on Harmonisation Good Clinical Practice guidelines and NHS Research Governance Framework. The clinical trial presented in Chapter 3 additionally received approval from the Brent Research Ethics Committee (REC), the Medicines and Healthcare products Regulatory Agency (MHRA) and the Health Research Authority (HRA).

Chapter 3: Therapeutic Alliance in Psilocybin Therapy for Depression

3.1 Background

Over the past decade, psychedelic-assisted therapy research has re-emerged with a growing body of evidence supporting its efficaciousness for a wide range of psychiatric and neurological conditions, including treatment resistant and major depressive disorder (MDD) (Carhart-Harris et al., 2021; Carhart-Harris et al., 2016; D'Souza et al., 2022; Davis, Barrett, May, et al., 2021; Falchi-Carvalho et al., 2024; Goodwin et al., 2022; Goodwin et al., 2025; James et al., 2024; Muttoni et al., 2019; Palhano-Fontes et al., 2019; Raison et al., 2023; Romeo et al., 2020; Rosenblat et al., 2024; Sloshower et al., 2023), anxiety related to life-threatening illness (Griffiths et al., 2016; Holze et al., 2023; Ross et al., 2016; Yu et al., 2021), bipolar II disorder (Meshkat et al., 2024), tobacco addiction (Johnson et al., 2014; Johnson et al., 2017), alcohol dependence (Bogenschutz et al., 2015; Bogenschutz et al., 2022), obsessive-compulsive disorder (Moreno et al., 2006), anorexia nervosa (Peck et al., 2023), cluster headaches (Schindler et al., 2022), and migraines (Schindler et al., 2021). The present study includes analyses of data from a double-blind randomised controlled trial (DB-RCT) which compared psilocybin-assisted therapy to six weeks of daily ingestion of a selective serotonin reuptake inhibitor (SSRI) antidepressant, escitalopram (Carhart-Harris et al., 2021) for MDD. While improvements on primary depression outcome were present in both treatment arms and statistically indistinguishable, the two doses of psilocybin with psychotherapeutic support sessions resulted in fewer side-effects and more wide-ranging improvements across secondary outcomes. Given these findings, alongside the growing evidence base for the efficacy of psychedelic-assisted therapy, there is a need to better understand its therapeutic mechanisms of action.

Extant research suggests that the quality of the acute psychedelic experience is predictive of psychedelic-assisted therapy's positive therapeutic effects (Romeo et al., 2021; Roseman et al., 2018). To date, the most extensively researched dimension of the acute psychedelic experience is the so-called 'mystical-type' or 'peak' experience, which includes deeply felt positive mood, ineffability, a sense of sacredness and unity, and transcendence (see Johnson et al., 2019). Several studies have provided evidence for the role of the mystical-type experience as a predictor of positive treatment outcomes following psychedelic-assisted therapy (Bogenschutz & Johnson, 2015; Carhart-Harris et al., 2018; Garcia-Romeu et al., 2014; Griffiths et al., 2016; Johnson et al., 2017; Roseman et al., 2018; Ross et al., 2016; for reviews, see Romeo et al., 2021 or Kangaslampi, 2023).

Beyond mystical-type experiences, recent prospective research (Roseman et al., 2019) and published accounts of trial participants' psychedelic therapy experiences (Gasser et al., 2015; Watts et al., 2017), have also highlighted the importance of emotional breakthrough, i.e. experiencing emotional release or catharsis in relation to difficult or previously inaccessible emotions or memories. Such processes and resulting personal and interpersonal insights are therapeutic mechanisms well established within traditional psychotherapeutic schools (Foa & Kozak, 1986; Greenberg & Pascual-Leone, 2006; Pascual-Leone, 2018; Samoilov & Goldfried, 2000). This view is also in line with well-established psychodynamic theories explaining psychedelic effects through the weakening of ego boundaries, granting access to previously unconscious material (Buchborn et al., 2023; Grof et al., 2008). Although naturalistic survey-based data has found higher levels of emotional breakthrough to be associated with improved mental health (Roseman et al., 2019; Spriggs et al., 2021), the role of emotional breakthrough experiences has not yet been evaluated within the context of controlled psychedelic-assisted therapy.

While the importance of acute psychedelic effects for treatment outcomes is well-established, far less research has been conducted on the role of contextual and psychosocial components of psychedelic-assisted therapy that may promote the subjective experiences shown to be supportive of clinical improvements. This includes the relationship between the individual receiving psychedelic therapy and the treatment provider(s) i.e. the 'guides' or therapists, which has been theorized to play a critical role for the outcomes of psychedelic therapy (Breeksema et al., 2020; Grinspoon & Doblin, 2001; Grof et al., 2008; Johnson et al., 2008; Nayak & Johnson, 2021; Richards, 2017; Watts & Luoma, 2020). The relationship between therapist and patient is recognised to be of fundamental importance across different psychotherapeutic models (Baier et al., 2020; Horvath, 2000; Lemma, 2024), commonly operationalized as 'therapeutic alliance' - i.e. the presence of a collaborative relationship that includes agreement on treatment goals/tasks and a positive emotional bond (Bordin, 1979). Extensive evidence has shown therapeutic alliance to be an important predictor of treatment outcomes in psychotherapy (for a review, see Baier et al., 2020), which can be best understood as a dynamic phenomenon that is sensitive to change over the course of therapy; with a time-lagged bidirectional and reciprocal relationship with symptom improvements (Falkenström et al., 2013; Labouliere et al., 2017; Morgan et al., 2023).

Despite extensive theoretical support, to our knowledge no quantitative research has been published evaluating whether the quality of the therapeutic relationship is predictive of psychedelic therapy outcomes, or of acute psychedelic experiences (e.g., mystical-type or emotional breakthrough experiences). Similarly, no studies to date have examined the potential bidirectional nature of this relationship, i.e. whether psychedelic experiences may conversely be associated with subsequent improvements in the therapeutic relationship, as several authors

have suggested previously (Fischer, 2019; Grinspoon & Bakalar, 1986; Grinspoon & Doblin, 2001).

The present study uses data from a published DB-RCT (Carhart-Harris et al., 2021) in which individuals with MDD received two treatment sessions of psilocybin (25mg) therapy plus six weeks of daily placebo or two treatment sessions with a de facto placebo and therapy and six weeks of daily escitalopram. Both arms additionally included three in-person visits and several remote visits for psychological preparation and integration. Due to our hypotheses regarding the mediating role of therapeutic alliance in mediating the quality of the psychedelic experience and subsequent clinical outcomes, we chose to focus specifically on the psilocybin condition, but analyses of the escitalopram arm are made available in the supplementary material of the published article (Murphy et al., 2021). Our primary aims were to:

1: Examine whether the quality of the acute experience (specifically, mystical-type experiences and emotional breakthrough) would mediate the effect of the therapeutic relationship on depression outcomes.

2: Explore potential bidirectional time-lagged relationships between the strength of the therapeutic relationship, the acute experience (mystical-type experience and emotional breakthrough) and changes in depression scores (measured via the 16-item self-rated Quick Inventory of Depressive Symptomatology or ‘QIDS’) from the first to the second psilocybin dosing session.

3.2 Methods

3.2.1 Trial Oversight

This randomised controlled trial comparing the effects of psilocybin and escitalopram for major depression received approval from the Brent Research Ethics Committee (REC), the Medicines and Healthcare products Regulatory Agency (MHRA), the Health Research Authority (HRA), and the Imperial Joint Research Compliance (study sponsors) and General Data Protection Regulation offices. All clinical visits took place at the National Institute for Health Research (NIHR)-funded Imperial Clinical Research Facility. The psilocybin for this trial was provided by COMPASS Pathways and the placebo tablets by the Pharmacy Manufacturing Unit at Guy's and St. Thomas' Hospital.

3.2.2 Participants

For detailed information about recruitment and screening procedures, see Carhart-Harris et al. (2021). The trial was advertised to General Practitioners via the NIHR Clinical Research Network and to the public online, recruiting men and women aged 18 to 65 years old suffering from depression. An initial telephone screening was followed by a remote Hamilton Depression assessment (HAM-D) (Hamilton, 1960), with a score of 17, indicating moderate to severe MDD being required for inclusion. Other exclusion criteria were: An immediate family or personal history of psychosis, major physical health conditions, a history of high risk suicide attempts, pregnancy, contraindications to SSRIs or magnetic resonance imaging (MRI), having failed a previous full course of escitalopram or having already taken psilocybin for the purposes of therapy, and a suspected or known presence of a psychiatric condition that could jeopardise rapport with the study team e.g., complex trauma or emotionally unstable personality disorder.

The final screening stage was a face-to-face visit involving physical and psychiatric assessments with the study clinicians. Subsequently, the participants met with their two guiding therapists for one hour. Discussion topics included current difficulties, salient early life experiences, family and interpersonal history, previous trauma and prior experience with psychotherapy. All participants withdrew from psychiatric medication for at least two weeks before starting the trial (see Table 3.1 for detailed demographics) and psychotherapy for at least four weeks.

3.2.3 Design

This was a phase II, double-blind, two-armed, randomised controlled trial. Participants were randomised either to an 'escitalopram arm' or to a 'psilocybin arm'. The current analyses will focus primarily on the latter arm, but full trial procedures and main clinical results for both arms have been reported in Carhart-Harris et al. (2021). See Figure 3.1 for an overview of the study design and clinical contact.

Each participant was assigned two guides. These were trained or training clinical psychologists, psychotherapists or psychiatrists with therapy experience. One of the pair was assigned the role of 'main guide' and was present in all six of their face-to-face visits and five calls post-screening (see Figure 3.1 for all clinical contacts). One of the two guides could be a clinical trainee if accompanied by an experienced mental health professional. In keeping with standard practice in psychedelic-assisted therapy (Grinspoon & Doblin, 2001; Grof et al., 2008; Johnson et al., 2008; Nayak & Johnson, 2021; Richards, 2017), the therapeutic protocol used in this trial consisted of preparation, support during psilocybin sessions, and integration. Principles of Acceptance and Commitment Therapy and psychological flexibility (Hayes et al., 2012) provided a particular source of inspiration for the therapy team, where the latter

construct, in particular, has been shown to be an important mediator of therapeutic outcomes in psychedelic-assisted therapy (Close et al., 2020; Davis et al., 2020; Zeifman et al., 2020). A psychedelic-specific therapy model, informed, in part, by ACT, emerged during the trial, and is referred to as The ACE model (Watts & Luoma, 2020). The ACE model emphasises building trust between participants and their guides, engaging with and accepting difficult emotions (in contrast to experiential avoidance), connecting to personal meaning and values and giving mindful awareness to embodied experiences (Watts & Luoma, 2020). Guides were encouraged to support participants in a non-directive and open manner, showing unconditional positive regard throughout (Rogers, 1951).

Approximately one week (7 to 10 days) prior to the first psilocybin dosing session guides rang participants (Check-in Call) to discuss practicalities, answer questions and to discuss the music playlist. In visit 1 ('Prep') all participants were given approximately five hours of preparation by their guides for the next day's psilocybin session. A primary aim of the preparation session was building trust and rapport, setting intentions and sharing information about psychedelic experiences. Emphasis was placed on ideas of moving towards difficult experiences and painful content. Prior consideration was given to how the guides would support the participants during the session e.g., thinking about how the participant might ask for help or what physical contact they would be comfortable with and agreed parameters for this were set between participant and guides ahead of the session itself.

During visit 2 (Dosing Day 1 [DD1]), participants in the psilocybin arm were given 25mg of psilocybin and participants in the escitalopram arm were given 1mg of psilocybin, accompanied and supported by their two guides throughout the day. All participants were informed that they would be given psilocybin without specifying the dosage, aiming to

standardise expectations. During the dosing sessions, participants wore eye masks and earphones through which they listened to a pre-selected playlist. This playlist was informed by research demonstrating the influence of music on the subjective experience and clinical outcomes (Kaelen et al., 2018). The guides provided the participant with psychological support throughout the day, while participants were encouraged to direct their attention inwards and share their experiences towards the end of the day, if they wished.

At the end of the dosing day, patients on the psilocybin arm were provided with a three-week course of placebo capsules, while patients in the escitalopram arm were given capsules containing 10mg of escitalopram. All patients were instructed to take these every morning for the duration of the trial. The morning after dosing, participants returned for an in-person 'integration' session (visit 3), where they discussed their psilocybin experience with their guides for two to three hours. Integration sessions involved open and attentive listening to participants' accounts of their experiences and reflections. The role of the guide during integration is to provide compassionate support and recognition of any psychological insights or changes. Visualisation exercises were used as a preparation and integration tool to support processes of attuning to their bodies, moving towards difficult emotions and connection to self and others, details of which can be found in the original publication on the ACE model (Watts & Luoma, 2020). Patients had the option of weekly one-hour integration or therapy calls with their main guides for the duration of the trial, as clinically indicated.

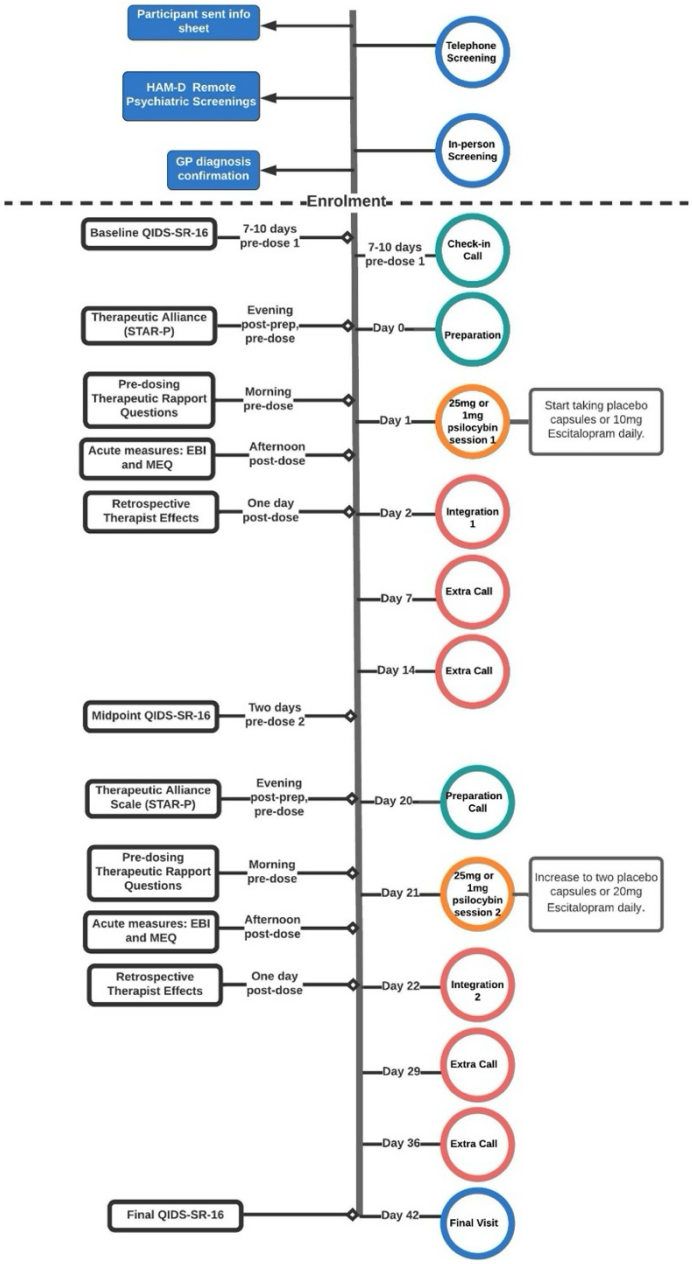


Figure 3.1 Flowchart Outlining Study Procedures. After the six-week key endpoint, participants completed remote monthly follow-up assessments until six months post-study. The dotted line separates pre-enrolment screening procedures (above line) from post-enrolment study procedures (below line). This figure has been reproduced with permission from Murphy et al. (2022). Info Sheet: Participant Information Sheet, HAM-D: 17-item Hamilton Depression Scale (clinician-rated), GP: General Practitioner, STAR-P: Scale To Assess the Therapeutic Relationship (participant-rated version), QIDS-SR-16: 16-item Self-Reported Quick Inventory of Depressive Symptomatology (primary outcome), EBI: Emotional Breakthrough Inventory, MEQ: Mystical Experience Questionnaire

Three weeks after the first psilocybin session (DD1), patients had a second 25mg (psilocybin arm) or 1mg (escitalopram arm) psilocybin dosing day (DD2; visit 4) and a next day integration session for two to three hours (visit 5), preceded by a shorter preparation call

over the phone. Patients in both arms were instructed to start taking two tablets every day, increasing the escitalopram dose to 20mg for the escitalopram arm.

Three weeks after the second integration session, patients returned for a three-hour final visit (visit 6; final follow-up [FFU]). This was their final formal integration with their guides within the 6-week trial, where they could discuss their experience of the trial and their current mood state. After performing key assessments, patients and clinicians were unblinded at this key endpoint so that the clinical team and patients could consider future treatment and support.

3.2.4 Measures

Participant information. Age, gender, ethnicity, education, employment, and clinical history including illness duration, past psychotherapeutic and pharmacological treatments were collected at screening.

Primary outcome. The 16 item self-rated Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 2003) was used to assess changes in depression severity (range of scores = 0-27). The QIDS was administered at three timepoints: (a) baseline, seven to ten days ahead of the first psilocybin session; (b) mid-treatment, three weeks after the first dosing and two days ahead of the second psilocybin session; (c) post-treatment/primary endpoint, three weeks after the second psilocybin session.

Therapeutic Relationship. The participant-rated Scale To Assess the Therapeutic Relationship (STAR-P) (McGuire-Snieckus et al., 2007) was used to assess the therapeutic alliance (specifically the constructs of positive collaboration, positive clinician input and non-

supportive clinician input) one-day pre-dose one and one-day pre-dose two. A self-constructed single-item measure of rapport ("*I have a good relationship with the main person/people who will look after me during the upcoming experience")* rated on a 0-100 Visual Analogue Scale (VAS) assessed the extent of rapport in the hours immediately before the psilocybin session, part of the Psychedelic Predictor Scale (Haijen et al., 2018). The term "therapeutic rapport" is sometimes used synonymously with "therapeutic alliance", albeit with a more specific stress on the positive nature of the emotional bond between the therapist and patient (Leach, 2005).

Acute subjective effects. On the afternoon of each dosing day, after psychedelic effects had worn off, participants completed the Mystical Experience Questionnaire (MEQ) (Barrett et al., 2015), which assesses mystical-type peak experiences using a 6-point Likert scale, as well as the Emotional Breakthrough Inventory (EBI) (Roseman et al., 2019), a 6-item (0-100 VAS) measure of cathartic release and resolution of difficult emotions or trauma.

3.2.5 Statistical Analysis

Primary Confirmatory Analysis. Longitudinal path modelling was employed to test the primary hypothesis, that therapeutic alliance would affect treatment outcomes by modulating the intensity of acute subjective effects. Based on previous research (Roseman et al., 2019; Roseman et al., 2018), mystical-type (MEQ) and emotional breakthrough experiences (EBI) were chosen as acute predictors of depression outcomes. Therapeutic alliance was measured on the day before each psilocybin session using the STAR-P. The single-item participant-rated measure of their felt rapport with their guides was taken within three hours prior to dosing. These values were included in the path model to account for variation in therapeutic rapport experienced by participants on the day of the session.

To simplify the analysis across the two separate psilocybin sessions while still considering all available data the respective maximum MEQ and EBI score across the two sessions was used to predict depression outcomes. Due to expected multicollinearity between the EBI and MEQ (r = .61 across both sessions), and to reduce model complexity, separate models were fitted including maximum EBI and MEQ scores, respectively, as well as the relevant STAR-P and Rapport scores (i.e. from the same respective dosing day on which the higher EBI or MEQ score was reported). Models with the same structure, including maximum EBI and MEQ scores, were constructed and analysed for subjects in the escitalopram arm (Supplementary Figure A3.1).

Secondary Exploratory Analyses. To investigate time-lagged reciprocal relationships between therapeutic relationship, acute psychedelic effects, and depression outcomes, additional (near-) saturated sequential mediation analyses were conducted for the first and second psilocybin session, a special case of path model in which all possible paths between all variables are specified. Saturated models reproduce the data perfectly but are also more susceptible to random noise in the data. The specification of all possible paths between variables makes this type of model especially useful for exploratory analyses that are not hypothesis driven. For both the first and second session, covariates included therapeutic alliance, rapport, MEQ and EBI (in separate models to mitigate multicollinearity issues and reduce model complexity). Outcomes in both sessions included depression severity at the key endpoint, corrected for baseline depression severity in case of the first, and intermediate depression severity in case of the second psilocybin session. As an additional outcome of the first psilocybin session, therapeutic alliance ahead of the second session was included to assess whether participant experiences during the first psilocybin session would impact the subsequent therapeutic relationship and thereby indirectly affect the second psilocybin session.

Additional paths between baseline (or in the case of session two, intermittent) QIDS scores and other included covariates led to (near-) saturation of the models, taking a general shape as displayed in Figure 3.2.

For all path analyses, robust maximum likelihood (RML) estimation was chosen as the estimation method, since all endogenous variables were continuous. Following the recommendation by Kline (2015), multiple indicators of model fit are reported for confirmatory analyses, including model Chi-Square/df, Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR). Simulation studies have shown that small sample sizes lead to an overestimation of fit for Chi-square, and an underestimation of fit for CFI and RMSEA (Shi et al., 2019), the latter thus being more conservative indicators in the present study. Thresholds for acceptable and good fit were taken from the extant literature, where less stringent cut-offs were chosen for RMSEA and SRMR to account for sample size biases (Awang, 2012; Hair et al., 2010; Hooper et al., 2008). Effect strengths of standardized regression coefficients were interpreted following Acock (2008), $\beta < 0.2$ being weak, $0.2 < \beta < 0.5$ moderate, and $\beta > 0.5$ a strong effect.

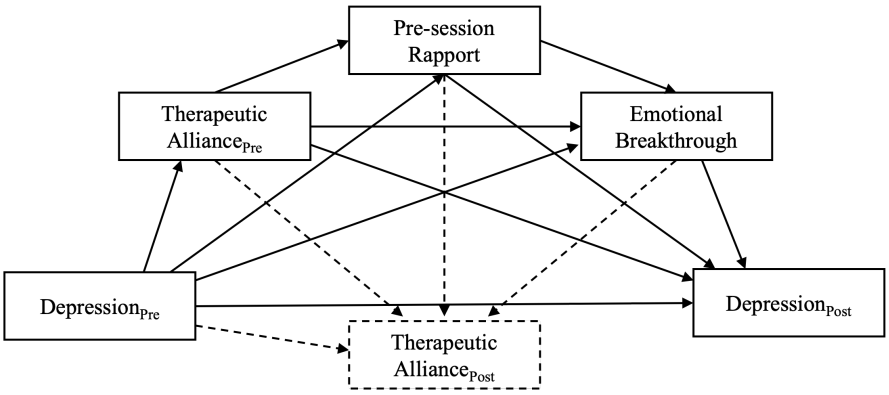


Figure 3.2 Structure of Exploratory Path Models displaying the general path structure of (near) fully saturated sequential mediation models testing the effect of therapeutic alliance on depression outcomes via the acute psychedelic experience. Models were repeated once for each of two dosing sessions, and once for emotional breakthrough and mystical-type experiences in place of the acute mediator, resulting in a total of four models. Dashed lines apply only to Dosing Day 1 (DD1) models, where subsequent alliance was added as an outcome. The solid-lined model is completely unrestricted, meaning that all possible paths between all variables are specified. This figure has been reproduced with permission from Murphy et al. (2022).

3.3 Results

3.3.1 Demographic Information

Approximately 1000 individuals were screened by telephone and/or email. 891 did not meet inclusion criteria and 50 chose not to participate. 59 participants with moderate-severe major depressive disorder were enrolled onto this trial. Participants were randomised to one of two groups: 30 into the psilocybin arm and 29 into the escitalopram arm. As the analyses in this study focus solely on the psilocybin arm, demographics for this sub-group are provided in table 3.1 below.

One participant has been excluded from this analysis because they did not comply with required restrictions on other substance use throughout the trial. Other protocol deviations include two participants who were unable to complete their second psilocybin dosing and integration visits due to Covid-19-related restrictions, and one participant who stopped taking their placebo tablets after guessing their content. The nature of the respective protocol

deviations for these participants were considered unproblematic for the present analyses and were thus not excluded.

Table 3.1 Demographic Information of Participants in the Psilocybin Arm of the Trial

Overall	
Total Patient Number Included in analysis	29
Total Patient Number Excluded from analysis	1
Demographics of those included	
Age, years - mean, SD (range)	42.8, 11.6 (21-64)
Females, number (%)	11 (38)
Caucasian Ethnicity, number (%)	27 (93)
Employment status - number (%)	
Employed	20 (69)
Unemployed	7 (24)
Student	2 (7)
University-level education, number (%)	22 (76)
Past psilocybin use, number (%)	7 (24)
Weekly alcohol (UK units) - mean, SD (range)	4.8, 5.4 (0-20)
Clinical	
Illness duration, years - mean, SD (range)	22.2, 10.9 (3-44)
HAMD- 17 scores at pre-treatment baseline -mean, SD (range)	19.2, 2.3 (16-23)
QIDS-16 scores at pre-treatment baseline - mean, SD (range)	14.7, 3.9 (7-23)
No. past psychiatric medications - mean, SD (range)	2.2, 1.7 (0-6)
Discontinued psychiatric medication for trial, number (%)	11 (38)
Past psychotherapy, number (%)	27 (93)

3.3.2 Confirmatory Analysis: Therapeutic Alliance Predicts Depression via Psychedelic Effects

As displayed in Figure 3.3, depression severity at the key endpoint was significantly predicted by both EBI and MEQ scores, but the standardised effects were slightly larger for EBI ($\beta = -0.56$, $p = .03$) as compared with MEQ ($\beta = -0.45$, $p = .04$) scores, suggesting that emotional breakthrough was a more reliable predictor of depression improvements in this trial,

than MEQ assessed 'mystical-type experience'. This difference was also reflected in a higher amount of explained variance in the final depression severity outcome in a model that included the EBI, vs one that replaced it with the MEQ: $R^2 = 0.42$ vs 0.32, respectively.

Table 3.2 Recommended and Actual Fit Indices for Confirmatory Path Models

	Recommended fit		Actual fit	
Fit index	Acceptable fit	Good fit	EBI	MEQ
CFI	> .90	> .95	.980	.929
χ^2 /df	< 3.0	< 2.0	1.18	1.78
RMSEA	< 0.10*	< 0.05	.082	.078
SRMR	< 0.10*	< 0.05	.092	.092

Note. CFI: Comparative Fit Index, χ2: Chi-square test statistic, df: degrees of freedom, RMSEA: Root Mean Square Error of Approximation, SRMR: Standardized Root Mean Square Residual; *conventionally, values of 0.8 are considered acceptable for RMSEA and SRMR. A more liberal cutoff was chosen due to the small sample size.

After subtracting the amount of variance explained by baseline depression severity alone, the EBI-based model explained 42% - 12% = 30% and the MEQ-based model explained 32% - 12% = 20% of variance in depression severity at the key endpoint. In both cases, the cumulative indirect effect of STAR-P on depression outcome was significant (β = -0.22, p = .02 for EBI-based model; β = -0.19, p = .03 for the MEQ-based model). Both models had acceptable to good fit on all estimated fit indices.

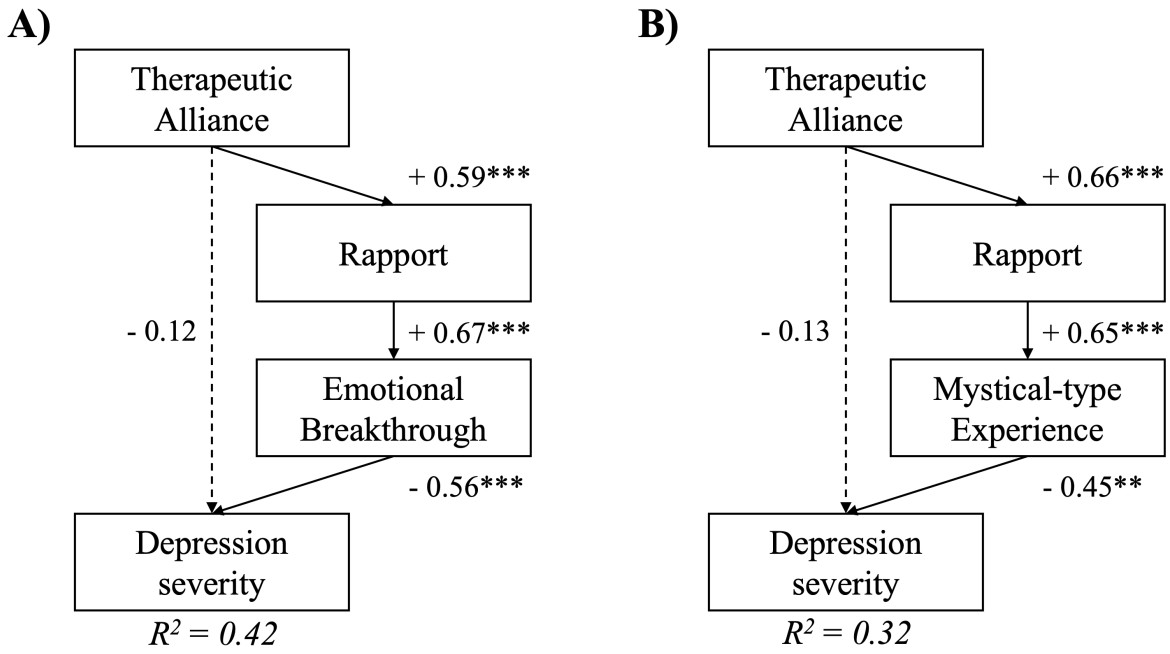


Figure 3.3 Confirmatory Path Models testing the primary hypothesis that therapeutic alliance would lead to better depression scores 6 weeks following psychedelic-assisted psychotherapy. Serial mediation of therapeutic alliance via pre-session rapport and A) Emotional Breakthrough and B) Mystical-type experiences were supported by the models. Depression severity at the 6-week Endpoint was adjusted for baseline depression scores ($p > .1$, not displayed in the figure), which by itself accounts for $R^2 = 0.12$, i.e., 12% of variance in the outcome. Numbers represent standardised regression coefficients for significant (solid) and non-significant (dashed) paths. This figure has been reproduced with permission from Murphy et al. (2022).

*** indicates $p < .001$

3.3.3 Secondary Exploratory Analyses: Time-lagged Bidirectional Effects.

Results for the near-saturated mediation models for the first psilocybin session are displayed in Figure 3.4. The EBI ($\beta = -0.65$, $p < .001$) significantly mediated the effect of therapeutic alliance on depression severity but the same was not quite true for the MEQ ($\beta = -0.39$, $p = .06$). Therapeutic alliance ahead of the second psilocybin session was significantly affected only by EBI ($\beta = 0.79$, $p < .001$), but not MEQ scores ($\beta = -0.02$, $p = .94$).

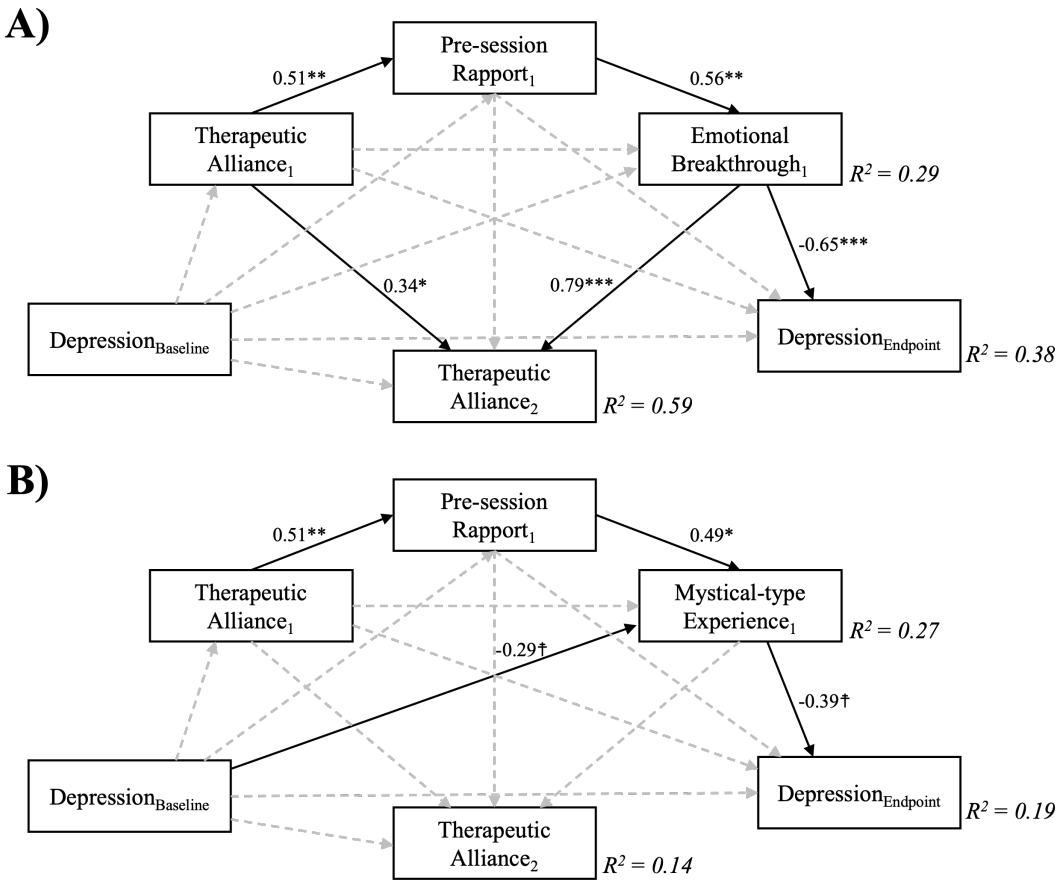


Figure 3.4 Near-saturated Exploratory Sequential Mediation Models exploring the relationship between therapeutic alliance during the first psilocybin session and depression scores six weeks following a two-dose course of psychedelic-assisted psychotherapy. Mediation of therapeutic alliance via pre-session rapport and A) Emotional Breakthrough (EBI) and B) Mystical-type Experiences (MEQ) were supported by the models in the case of depression severity, but not for intermediate therapeutic alliance measured ahead of the second psilocybin session, which was only predicted by EBI scores. Depression severity at 6 weeks was controlled for baseline depression scores, which by itself accounted for $R^2 = 0.12$, i.e., 12% of variance in the outcome. MEQ, but not EBI scores were affected by baseline depression severity, although only at trend level. Numbers represent standardised regression coefficients for significant (solid, $p > .1$) but not non-significant (dashed) paths. This figure has been reproduced with permission from Murphy et al. (2022).

† indicates $p < 0.1$, * $p < .05$, ** $p < .01$, *** $p < .001$

While 59% of variance in STAR-P scores was explained in the EBI model, the MEQ-based model only explained 14% of variance in STAR-P scores, which approximately corresponds to the amount of variance accounted for by baseline STAR-P scores. A trend-level relationship was found between baseline QIDS scores and MEQ scores, meaning that higher baseline depression severity was associated with lower mystical-type experience scores for the first psilocybin session ($\beta = -0.29$, $p = .09$).

Results for the saturated mediation models for the second session are displayed in Figure 3.5. When controlling for intermediate QIDS scores, only MEQ (β = -0.45, p = .002) but not EBI (β = -0.18, p = .27) scores significantly affected final depression outcomes. Instead, significant direct effects between therapeutic alliance and depression outcomes emerged for each model (β = -0.33, p = .049; β = -0.31, p = .033, for MEQ and EBI-based models, respectively). A large overall amount of variance in final depression outcomes was explained in each of the fully saturated mediation model (R^2 = 0.67, and 0.57), but it is important to note that the correlation between depression severity at the intermediate and the final endpoints was very high at r = 0.74, thus already accounting for 0.74^2 = 55% of variance. The implication is that most of the mediation occurs in relation to the first dosing session, after which depression severity prior to session two is a strong predictor of depression severity at the six-week endpoint. The additional amount of variance in final depression severity outcomes explained by inclusion of other covariates than midline depression was thus only approximately 67% - 55% = 12% for the MEQ-based model, while the inclusion of EBI scores and other covariates during the second session only explained 65-55 = 10% of additional variance.

Significant negative effects of midline QIDS on therapeutic alliance (β = -0.49, p = .004), as well as pre-session rapport (β = -0.49, p = .036) were revealed both in the EBI- and MEQ specific models, meaning that higher depression severity at the intermediate (3 weeks post-session 1) timepoint was associated with worse therapeutic alliance and rapport ahead of the second session. Again, this finding highlights the bidirectionality of causation between therapeutic relationship and treatment effects, as well as the importance of processes leading up to and including dosing session one as being the major determinants of eventual outcomes at the study endpoint.

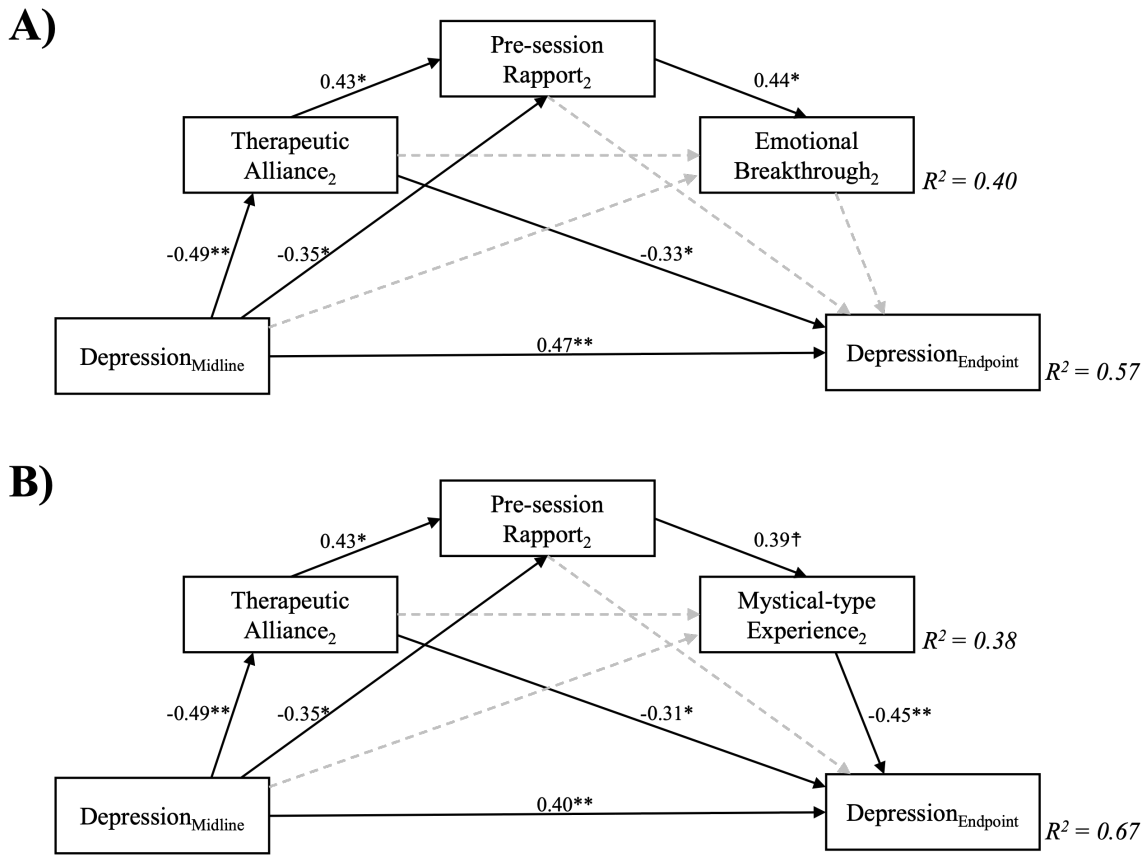


Figure 3.5 Fully Saturated Exploratory Sequential Mediation Models exploring the relationship between therapeutic alliance during the second psilocybin session and depression scores 6 weeks following a two-dose course of psychedelic-assisted psychotherapy. Sequential mediation of therapeutic alliance via pre-session rapport and B) Mystical-type Experiences, but not A) Emotional Breakthrough was supported. Depression severity at 6 weeks was controlled for midline (3 weeks post-first dose) depression scores, which by itself accounted for 55% of variance in the outcome. Greater midline depression severity significantly predicted worse therapeutic alliance and pre-session rapport scores. Decimal values represent standardised regression coefficients (β values) for significant (solid, $p > 0.1$) but not non-significant (dashed) paths. The subscript 2 refers to the second psilocybin session. This figure has been reproduced with permission from Murphy et al. (2022).

† indicates $p < 0.1$, * $p < .05$, ** $p < .01$, *** $p < .001$

3.4 Discussion

The importance of the therapeutic relationship in psychedelic-assisted therapy has long been treated as a matter of conventional wisdom, both traditionally and in contemporary research (Breeksema et al., 2020; Carhart-Harris & Nutt, 2017; Grof et al., 2008; Gukasyan & Nayak, 2021; Nayak & Johnson, 2021; Richards, 2017; Watts & Luoma, 2020) although it has never been established empirically. Here, via sequential path modelling, the predictive effects of therapeutic alliance on clinical outcomes via greater emotional breakthrough and 'mystical

type' experiences were shown in a trial of psilocybin-assisted therapy for depression. This constitutes the first empirical evidence demonstrating how acute psychedelic effects, previously established as critical to outcomes of psychedelic use (Johnson et al., 2019; Roseman et al., 2018; Watts et al., 2017), are modulated by the patient-therapist relationship in psychedelic-assisted therapy.

Initial confirmatory models found that depression severity at the six-week endpoint was significantly reduced as a function of the most intense emotional breakthrough and mystical type experience across the two dosing sessions and that these acute effects were in turn enhanced by better therapeutic alliance reported on the day before, and rapport in the minutes before dosing. A greater standardised effect on depression severity was seen for emotional breakthrough scores, reflected by a 10% larger amount of variance in final depression severity explained by mediation models including the EBI, compared to the MEQ. While the predictive value of the acute experience on clinical outcomes is in line with previous research (for a review, see Romeo et al., 2021), this finding challenges the historical focus on mystical-type experiences in research on the psychological determinants of psychedelic outcomes. The present study may thus inform the contemporary scientific discourse related to overcoming 'mysticism' in psychedelic research (Sanders & Zijlmans, 2021) as well as the questioned necessity of the subjective psychedelic experience for enduring therapeutic effects (Olson, 2020; Yaden & Griffiths, 2020), which has led to an increasing interest in developing non-hallucinogenic analogues of psychedelic compounds (Cameron et al., 2021).

Findings of the exploratory analysis of session-specific and bi-directional effects indicate the need for process- and relationship-sensitive adaptive treatment approaches in psychedelic trials. This includes for example session-specific differences in the mechanistic

role of acute psychedelic effects: While in the first psilocybin session, emotional breakthrough was the most potent predictor of subsequent improvements in depressive symptoms and mystical-type experiences only reached trend-level significance, this pattern was reversed for the second dosing session. This provides some tentative support for a stage-based approach to treatments involving more than one psychedelic dose, as suggested e.g., by the 'Grofian model', which suggests that during psychedelic states, a 'working through' personal, biographical material commonly precedes experiences of transpersonal nature (Grof, 2008). It is also notable that higher baseline depression was associated with lower mystical experience scores but had no impact on emotional breakthroughs during the first session. A possible explanation for this is that more severely depressed patients may often have a more complicated history of adversity, necessitating a stage-wise process of first working through personal material before progressing to a transpersonal stage.

Reflecting the results of the confirmatory analysis, therapeutic alliance, mediated via pre-session rapport, explained a statistically significant amount of variance in both mystical-type and emotional breakthrough experienced during this first dosing session. This highlights the value of preparatory activities that allow for the formation of a therapeutic relationship ahead of any substance sessions. Importantly, during this first dosing session, the intensity of acute effects, particularly emotional breakthrough experiences, not only predicted better depression outcomes, but also had a significant effect on the level of therapeutic alliance assessed ahead of the second dosing session. This provides some preliminary evidence for a bidirectional relationship between the therapeutic relationship and acute intrasubjective psychedelic effects: A strong therapeutic alliance pre-session appears to support participants towards more intense mystical experiences and emotional breakthroughs, which, in the context of a containing and supportive environment, may be able to conversely reinforce and augment

the therapeutic relationship between participants and guides. This dynamic and reciprocal interplay between interpersonal processes and pharmacologically induced altered states of consciousness during psychedelic-assisted therapy offers compelling evidence for the existence of circular causal relationships – a co-evolution of individual and environment- as would be suggested by an enactive model of psychedelic effects (Fuchs, 2020; Fuchs, 2023; Meling & Scheidegger, 2023). Although not presented here in full, the absence of any significant effects of the therapeutic relationship on treatment outcomes in the escitalopram condition (Supplementary Figure A3.1) indicates that the observed psychosocial dynamics are furthermore a function of the psychedelic substance, thus highlighting the emergence of therapeutic processes from an interdependent matrix of biopsychosocial causal factors.

Limitations and future directions. An important limitation of the current study arises from the small sample size available for the present analyses. The path analyses applied here usually require large (N>100) sample sizes to be considered reliable (Kline, 2015); although rules-of-thumb for sample size estimations in structural equation modelling have been found to be insufficient (Wolf et al., 2013). Even though models consistently converged and showed acceptable fit, which is normally underestimated in small samples (Jackson, 2001), it is possible that the established parameter estimates are biased by participant characteristics specific to the trial. Future studies should therefore focus on replicating the causal pathways found here in larger samples from psychedelic trials or real-world psychedelic use. Another limitation of the present study lies in the assessment only of participant- but not clinician-rated therapeutic alliance, the latter having been found to be at least as (Bachelor, 2013) or even more predictive (Bickman et al., 2012) of psychotherapy outcomes. The concurrent measurement of alliance rated both by participants and guides may be particularly helpful for understanding what data will be best suited to optimally guide treatment choices. Including

guides as participants in future studies may also allow for the assessment of the guide's professional and personal experience, as well as demographic information, all of which might interact with patients' characteristics in the formation of the therapeutic relationship.

This is the first study to provide quantitative evidence supporting the importance of the therapeutic relationship in shaping both the acute psychedelic experience and subsequent treatment outcomes in a randomised clinical trial of psychedelic-assisted therapy. It is also the first study to validate the importance of emotional breakthrough experiences in mediating therapeutic outcomes in a clinical population. As pointed out previously (Kangaslampi, 2020), the nascent field of mechanistic studies in psychedelic research suffers from several methodological limitations, including the lack of appropriate testing of putative causal relationships. By implementing sequential mediation analyses on variables that were measured across successive time points, the current study was able to inform on causal relations in the treatment process, including time-lagged bidirectional effects across social and psychological constructs. The next chapter will apply similar methodologies to naturalistic psychedelic group experiences to explore the role of psychosocial factors beyond dyadic relationships.

Chapter 4: Psychedelic Communitas in Naturalistic Group Settings

4.1 Background

The 'biomedical revolution' of the 1970s and ‘80s led to an explosive infiltration of pharmaceutical interventions into psychiatric practice and the marginalization of previously favoured psychodynamic approaches, consequentially inviting the charge that clinical psychopharmacology offers an atomised, decontextualised, and revenue- rather than patient-centric approach to mental illness (Deacon, 2013; Kleinman, 1988; Kleinman & Cohen, 1991; Peele, 1981). Research on the therapeutic application of serotonergic psychedelics constitutes a curious outlier in this regard, considering the strong emphasis it places on the role of psychological, social, and cultural context of administration – 'set and setting' – for attaining therapeutic success (Carhart-Harris, Roseman, et al., 2018; Carhart-Harris, 2018; Hartogsohn, 2016, 2017; Leary et al., 1963). However, motivated by pragmatic and safety reasons, modern trials of psychedelic-assisted psychotherapy have almost exclusively employed individual, rather than systemic or group therapy approaches – consistent with dominant psychedelic therapy models of the 1950s-70s (Grof, 1980), although modern and historical exceptions exist (see Trope et al., 2019 for a historical review of psychedelic-assisted group therapy research). The focus on individual therapy, delivered in highly engineered clinical settings, may partially explain why contemporary psychedelic research has largely neglected one of the most prevalent factors impacting psychedelic effects *in natura*: the collective dimension of psychedelic use.

The socially constructive function of psychedelic use has been central in many cultures that developed customary or ritualised forms of consumption (Andritzky, 1989; Dobkin de Rios, 1984; Hunt & Barker, 2001; M. Winkelman, 2010), and can be inferred even from earliest

mentions and anthropological studies of indigenous usage (La Barre, 1938; Villavicencio, 1858). An inherently collective function of psychedelic use is also reflected in the plethora of approaches to psychedelic use that persists in contemporary cultures, ranging from dance-events ("raves") (Papadimitropoulos, 2009) to religious ceremonies conducted in ayahuasca churches (Tupper, 2008), to the ceremonial use of ayahuasca or psilocybin mushrooms at retreat centres (Rucker & Young, 2021; Ruffell et al., 2021). The number of people drawing on various types of these naturalistic settings by consuming psychedelic substances on their own behalf has been increasing rapidly in recent years (see also Figure 1.3, Matzopoulos et al., 2022; Palamar & Le, 2018; Yockey et al., 2020), often with self-medicative purposes (Hutten et al., 2019; Kettner, Mason, et al., 2019; Mason & Kuypers, 2018). The fact that naturalistic psychedelic use almost invariably occurs in collective settings raises the question how these substances acutely affect the experience of intersubjectivity - i.e. human interaction, relationality, shared emotional and cognitive states - and how such psychosocial dynamics might, in turn, act upon the psychological constitution of the individual.

A rapidly growing phenomenon that lends itself particularly well to the study of psychosocial effects of psychedelics can be found in psychedelic retreat settings. In countries where certain psychedelics remain legal, the global unmet demand for supervised and structured containers of psychedelic use has given rise to local industries dedicated to providing such experiences. Multi-day retreat programs, whether involving psilocybin truffles in the Netherlands, or ayahuasca in the Peruvian Amazon, typically consist of one or more guided psychedelic group sessions, commonly referred to as 'ceremonies'. While many psychedelic retreat providers utilise elements discovered to be useful in psychedelic therapy, such as tailored playlists for psychedelic sessions (Kaelen et al., 2018), many facilitators also draw from other therapeutic or spiritual traditions. These often include techniques aimed to structure

the relational dynamics amongst retreat participants and between participants and facilitators. A prevalent example are ‘sharing-round’ rituals (Fotiou, 2020; Gearin, 2015, 2016), often held both before and after ceremonies, during which participants are invited to articulate personally salient material, such as intentions for, or experiences during sessions. Controlled self-disclosure of feelings and thoughts, being fundamental for developing social relationships (Derlega & Chaikin, 1977), has been shown to elicit trust and reciprocity especially among 'passing strangers' (coming from different locations) (Rubin, 1975) and liking within groups (Collins & Miller, 1994). These ritualised and carefully moderated spaces for exchange may therefore facilitate the creation of intragroup cohesion and alliance with facilitators, the potential importance of which, although not yet investigated empirically, can best be understood in light of group psychotherapy research, where cohesion and therapeutic alliance are among the most powerful predictors of positive treatment-outcomes (Schnur & Montgomery, 2010). On an individual level, apart from rendering facilitators potentially more able to adequately react to difficult material arising during psychedelic sessions, disclosure of deeply personal, especially challenging, narratives or experiences, without others advising or judging, has been shown to improve emotion regulation and enhance self-acceptance (Farber, 2003; Hemenover, 2003; Kahn & Garrison, 2009), suggesting that sharing-rounds in psychedelic retreats might in themselves hold therapeutic value (Aranovich, 2020).

In addition to the relational processes commonly employed in preparation and aftercare of ceremonial psychedelic use, one can also expect the acute psychedelic state itself to be impacted by the presence of others. However, little to no quantitative empirical research exists on the intersubjective phenomenology of psychedelic states, which is striking considering the substantial body of literature indicating a crucial role of the acute psychedelic state mediating the long-term psychological outcomes of psychedelic substance use (Haijen et al., 2018;

Kettner, Gandy, et al., 2019; MacLean et al., 2011; Roseman et al., 2019; Roseman et al., 2018; Spriggs et al., 2021; Uthaug et al., 2019; Uthaug et al., 2018). Whereas psychedelic research has so far focussed largely on individual, i.e. intrasubjective drug effects, entry points into relational or 'intersubjective' aspects of shared altered states of consciousness can be found in studies on ritual and collective action. As proposed by Durkheim (1912), an important function of collective dancing, music listening, or music-making (which are commonly also employed in psychedelic group settings) lies in their ability to induce a synchronization of affect and behaviour among participants. This phenomenon, originally termed 'collective effervescence' (Durkheim, 1912) has been identified as a catalyst for the blurring of self-other boundaries, social affiliation and cooperation (Hove & Risen, 2009; Reddish et al., 2013; Tarr et al., 2014). Specifically, Páez et al. (2015) found increased perception of emotional synchrony in collective gatherings to elicit 'identity fusion', a process that implies a change in self-concept from a personal to a collective level. Identity fusion has been described as "a unique form of alignment with a group, one that entails a visceral feeling of oneness with the group" (Swann Jr et al., 2012, p.441), which, in concurrence with phenomena of synchrony, may explain how collective rituals often reinforce social connectedness and cohesion (Whitehouse et al., 2014).

The theory of identity fusion is conceptually linked to Victor Turner's (1969) notion of "spontaneous communitas", an experience of intense togetherness and shared humanity that temporarily transcends social structures. According to Turner, communitas occurs in situations such as rites of passage, where existing relational structures are lifted to allow for a transition into a new social configuration, mediated by an anti-structural and often ritualised 'liminal phase' of equality among community members. Communitas, thereby, involves a transgression or dissolution of norms that regularly govern structured or institutionalised relationships, placing the group that experiences it temporarily 'outside' of society. Unsurprisingly, modern

conceptions of communitas and liminal experience thus also include states of spontaneous fellowship during events such as natural disasters, revolutions, countercultural happenings, music or sport events (Turner, 2012), which suspend conventional social structures. Explaining how communitas may generate enduring changes beyond the acute liminal state, Olaveson (2001) discusses how the dialectic of communitas lies in the revitalizing function that this anti-structural state entails, owed to its creative potential: "In liminality, the state in which communitas occurs, culture is analysed into factors and freely recombined and experimented with (Turner & Turner, 1970). […] Anti-structure can thus be a positive and generative force (Turner, 2018), and is a condition in which myths, symbols, rituals, philosophy, and art are generated, which are templates for the periodical reclassification of reality and man's relationship to society, nature, and culture." (Olaveson, 2001, p. 106).

The concept of communitas thereby invokes a fascinating semblance to the transformative potential of psychedelic states, which analogously has been discussed as resulting from a temporary suspension of established hierarchical neurocognitive structures, allowing for less constrained recombination of thoughts, emergence of novel insights, and sometimes radical reorientation of the individuals' relationship to themselves, others, and reality at large (Carhart-Harris & Friston, 2019). While seeing the psychedelic state as a 'functional communitas of the brain' might be an overly-stretched analogy, Turner's concept of spontaneous communitas has indeed been applied to explain transformative collective experiences both in psychedelic rave culture (Tramacchi, 2000), as well as in psychedelic ceremonies (Lewis, 2008; Mantere, 2013; Roseman, 2019b), although not yet assessed quantitatively in this context.

The current study aimed to address the existing gap of knowledge and research instruments operationalizing relational processes pertinent to psychedelic experiences, providing a first comprehensive, quantitative assessment of psychosocial mechanisms underlying collective psychedelic use. For this purpose, a large prospective sample of psychedelic use to psychometrically is analysed here to validate an adapted psychedelic *Communitas Scale* (COMS), a measure of communitas specifically tailored to psychedelic group experiences. Construct and criterion validity are investigated through the COMS' relationship to: 1) validated measures of intersubjective experience and acute psychedelic effects; 2) 'set and setting', specifically its relational elements (identity fusion, self-disclosure, rapport with participants and facilitators); as well as 3) long-term psychological outcomes, including psychological well-being and social connectedness as primary outcomes, and depressive symptoms, trait anxiety, and interpersonal tolerance as secondary outcomes. Additionally, this chapter also includes results showing age-dependent effects of communitas in a subset of older adults (OA) (Kettner et al., 2024), and the role of communitas for changes in metaphysical beliefs (Timmermann et al., 2021).

4.2 Methods

4.2.1 Participants

This study involved web-based data collection from a self-selected opportunistic volunteer sample, consisting of participants in guided psychedelic group sessions, predominantly in retreat settings. Eligibility criteria were being 18 years or older, a good comprehension of the English language, and the intention to participate in a retreat, ceremony, or other guided experience involving the use of a classic psychedelic containing a 5-HT2A receptor agonist (e.g., psilocybin, DMT, mescaline, or LSD).

Participants were recruited following two dissemination strategies: Firstly, advertisements including a link to the study website (www.ceremonystudy.com) were posted and shared on psychedelic-related online fora (Reddit groups, Bluelight, and ayahuasca.nl), email newsletters (MAPS, Chakruna, and psychedelicexperience.net), and social media platforms (Twitter and Facebook). Secondly, retreat centres and facilitators of guided psychedelic experiences were contacted with information about the study, inviting them to advertise the study to their future clients. This mediated outreach strategy was chosen to maximise awareness of the study in the target population, and to facilitate the collective participation of multiple participants from a single retreat or ceremony group.

4.2.2 Design

A minimum of five surveys were completed by participants at different time points. A first baseline measurement took place two weeks before the psychedelic experience, followed by a second measurement up to three hours before. A third measurement took place on the day after the experience, in which subjective drug effects were assessed retrospectively. A fourth survey was completed on the day after leaving the ceremony or retreat location. Finally, the fifth, key endpoint survey was completed four weeks after the end of the psychedelic retreat or ceremony.

4.2.3 Measures

Participant information. Questions assessing demographic information, including age, gender, nationality, education, employment, income, ethnicity, and marital status, as well as frequency of lifetime psychedelic use and psychiatric history were assessed at baseline.

Experience details. Details of the upcoming experience included the type of substance expected to be used ("Psilocybin / magic mushrooms / truffles"; "LSD / 1P-LSD"; "Ayahuasca"; "DMT"; "5-MeO-DMT (Bufo)"; "San Pedro"; "Peyote"; "Iboga / Ibogaine"; self-specified option), the duration (in days) and number of psychedelic sessions of the retreat.

Outcome measures. As primary outcomes, the 14-item Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) (Tennant et al., 2007), the 8-item Social Connectedness Scale (SCS) (Lee & Robbins, 1995), and the Watts' Connectedness Scale (WCS) were used at baseline and the 4-week key endpoint to assess longitudinal changes in well-being and psychosocial health from before to after the psychedelic retreat. Total scores of the WCS, assessing general connectedness as an average across its three subscales, connectedness to others, self, and world, were included in analyses. Secondary outcomes included the self-report version of the Quick Inventory of Depressive Symptomatology (QIDS-SR-16, hereon referred to as the QIDS) (Rush et al., 2003) and the 6-item short form of the Spielberger Trait-State Anxiety Inventory (STAI) (Marteau & Bekker, 1992) trait subscale were included to measure changes in depressive symptoms and trait anxiety. Lastly, the Warm Tolerance subscale of the Interpersonal Tolerance Scale (IPTS) (Thomae et al., 2016) was used to assess changes in attitudes and openness toward people who hold different values or beliefs than one's own.

Trait predictors. Trait absorption was measured using 25 items of the Modified Tellegen Absorption Scale (MODTAS) (Jamieson, 2005), a previously identified predictor of acute psychedelic drug effects (Haijen et al., 2018; Studerus et al., 2012). Additionally, the *peer conformity* subscale of the Multidimensional Iowa Suggestibility Scale (Kotov et al., 2004) was included to assess potentially moderating effects of peer conformity on the relationship between intersubjective psychedelic effects and long-term outcomes

Metaphysical Beliefs. As a secondary outcome of interest, a novel 13-item measure of metaphysical beliefs was included. The Metaphysical Beliefs Questionnaire was validated in the present sample (Timmermann et al., 2021), revealing good internal consistency (Cronbach's alpha = .86) for a primary factor comprising nine 7-point Likert items. The included items assessed agreement with a heterogeneous range of beliefs and were summarised as 'non-physicalist' beliefs (NPB), such as *ontological transcendentalism* ("There exists another separate realm or dimension beyond this physical world that can be experienced and visited"), *non-naturalism* ("The universe obeys a unifying principle which is beyond any possible material or scientific explanation.") or *panpsychism* ("Mind, consciousness, or soul is a fundamental quality of all things in the universe, either animate or inanimate").

Preparedness – "set". The 12-item psychedelic predictor scale (Haijen et al., 2018) was used 3-24 hours ahead of the session to assess preparedness for the experience. A sub-score for the social setting pre-ceremony (from here on referred to as 'Rapport') was calculated as the sum of the items "*I have a good feeling about my relationship with the group/people who will be with me during the experience*" and "*I have a good relationship with the main person/people who will look after me during the upcoming experience*" from the psychedelic predictor scale. In the present sample, the Pearson correlation coefficient for the two items of this subscale was strong (r = 0.62). Additionally, a single-item pictographic identity fusion scale (IFS) (Swann Jr et al., 2009) was included to assess identity fusion with the group shortly before the session.

Acute subjective effects. To assess subjective drug effects, a combination of validated and self-constructed questionnaires was employed, to be completed within 24 hours after the day of the psychedelic session. These included: The 30-item Mystical Experience

Questionnaire (MEQ) (Barrett et al., 2015), including four subscales (mystical, positive mood, transcendence of time and space, ineffability); and the 6-item Emotional Breakthrough Inventory (EBI) (Roseman et al., 2019), assessing cathartic resolution of conflict or past trauma. To further assess psychosocial effects during the session, a short 5-item version of the Perceived Emotional Synchrony Scale (PESC) (Páez et al., 2015), assessing feelings of collective emotional entrainment and the pictographic IFS were included. Lastly, an 8-item Communitas Scale (COMS, see Fig 4.2) was adapted based on items previously used in the context of sports (McGinnis et al., 2012) and night clubs (Taheri et al., 2016), rated on a 7-point Likert scale. Two further self-constructed items were added, which assess the connection felt with another participant and with a facilitator during the experience, respectively. In order to assess the impact of emotional support delivered in the ceremonial setting, participants rated one further self-constructed item "*To what extent did the presence of emotionally supportive individuals influence the overall quality of your experience?*" on a 1-100 VAS.

Retreat experience. On the day after the retreat, an adapted version of the COMS and pictographic IFS were included, measuring both constructs in reference to the retreat as a whole, rather than just the duration of a single psychedelic ceremony. Additionally, the revised self-disclosure scale (RSDS) (Wheeless & Grotz, 1976) was used to measure self-perceived self-disclosure across six components (intended disclosure, positiveness, honesty, amount, relevance, and depth of disclosure), using a total of 18 items rated on a 7-point Likert scale which are summed into a total self-disclosure score.

4.2.4 Statistical Analysis

Data from all time points was imported and merged using the Statistics Toolbox or Matlab (Release 2019b) and was then exported for further analysis into RStudio (v1.2).

Psychometric validation of the COMS. Several heuristics were employed to investigate the factor structure and internal consistency among the eight items of the COMS. Visual examination of the scree plot and the 'Kaiser rule' (1960), which accepts as reliable factors those whose corresponding eigenvalue is larger than one, were applied. Complementary analyses included optimal coordinate and acceleration factor tests in order to identify an appropriate number of factors via non-graphical solutions (Raîche et al., 2013). The scale reliability was assessed via Cronbach's alpha and composite reliability - the latter being less prone to over- or underestimations of reliability at a population level (Raykov, 1998).

To assess construct validity, bivariate Pearson correlations were calculated between COMS scores, self-constructed items on participant and facilitator-connectedness, and the subscales of validated subjective experience measures taken at each ceremony (IFS, PESC, MEQ, CEQ, ASC-VE).

Changes in primary outcomes predicted by communitas. To test the primary hypothesis that communitas experienced during psychedelic group sessions would be predictive of changes in the primary outcomes well-being (WEMWBS), social connectedness (SCS), and general connectedness (WCS), Pearson-correlations were calculated between COMS, and baseline to key endpoint difference scores on the SCS, WEMWBS, and WCS. For participants who reported multiple ceremonies, the analyses considered the highest COMS score reported.

Additionally, two-sided pairwise t-tests were conducted for SCS, WEMWBS, and WCS to assess significance of changes from baseline to the key endpoint. The same procedure was repeated for the secondary outcomes trait anxiety (STAI), depression severity (QIDS), and interpersonal tolerance (IPTS).

Path analysis. To explore the causal structure of the assessed psychosocial factors, a longitudinal path analysis was conducted across the five collected timepoints, including individuals who partook in no more than one ceremony over the course of a retreat (N in analysis = 631). As a first step, an initial model was constructed considering the following variables: 1) Psychological trait absorption and demographics (age, gender) measured at baseline; 2) Identity fusion and rapport assessed hours before the psychedelic session; 3) Perceived emotional synchrony, communitas, identity fusion and 'perceived emotional support' during the session, assessed on the following day; 4) Self-disclosure, communitas and identity fusion in relation to the retreat as a whole, measured on the day after leaving the ceremony location; and 5) Psychological well-being and social connectedness as long-term psychological outcome variables, assessed 4 weeks later and controlled for baseline values. In this initial model (represented in Figure 4.1), regression paths were set so that each variable at time point t would predict each variable at time points $t + 1$ and $t + 2$, thereby accounting for uncaptured delayed effects. Additionally, theoretically motivated concurrent regression paths were allowed within timepoints 3) and 4) from 'perceived emotional support' and 'self-disclosure' to the remaining variables within the respective timepoint.

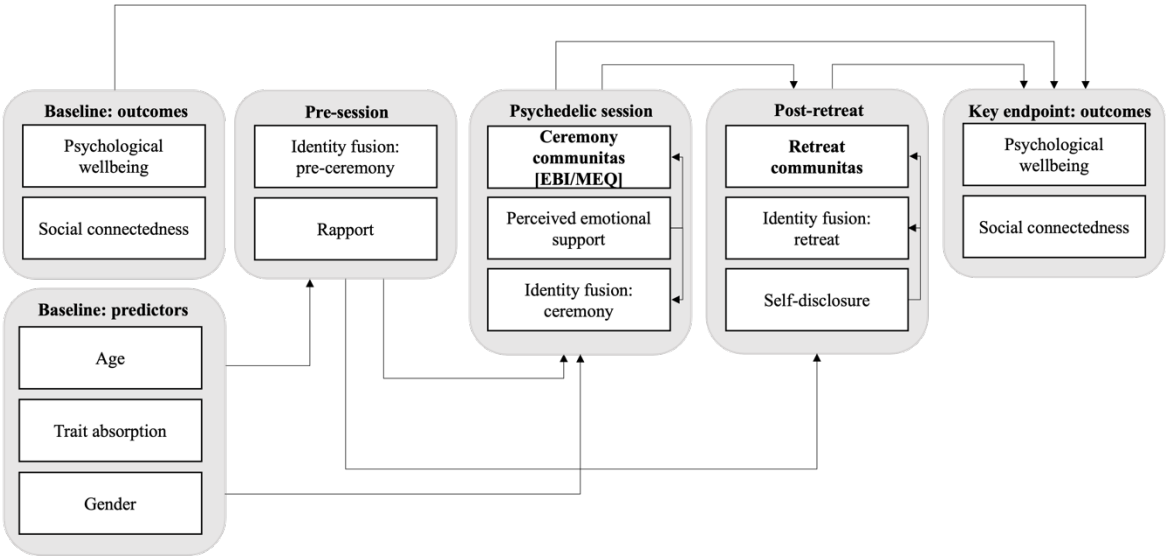


Figure 4.1 Initial Path Model showing hypothesised relationships of psychosocial variables during psychedelic retreat settings, measured across 5 time points. This figure has been adapted with permission from Kettner et al. (2021). EBI: Emotional Breakthrough Inventory; MEQ: Mystical Experience Questionnaire

To test whether the resulting structural role of communitas in the model was unique, the pruning process described above was then repeated after replacing acute COMS scores in the initial model with two measures of intrasubjective psychedelic effects, the MEQ and EBI.

Communitas as a predictor of change in older adults A post-hoc analysis was carried out on a subsample of 62 older adults (OA, aged ≥60 years) to assess whether communitas played a similar role for post-psychedelic psychological benefits regardless of age. The full analysis of this subsample is published elsewhere (Kettner et al., 2024). Participants were included in this analysis if they had completed at least the baseline and the post-session survey. OA were identified based on a reported age of ≥60 and a set of matched younger adults (YA) was selected using nearest neighbour matching via the *MatchIt* package implemented in R[1], matched for gender, education, psychiatric history, previous psychedelic use, baseline well-

[1] https://cran.r-project.org/web/packages/MatchIt/vignettes/MatchIt.html

being, and drug dose. By projecting the above variables in a multidimensional Euclidean space, MatchIt uses propensity scores based on k-nearest distance between given data points to pair participants across the OA and YA samples. Through this procedure, MatchIt can improve parametric statistical models for estimating treatment effects in observational studies and reduce model dependence. As a non-parametric one-to-one matching algorithm, it implements the suggestions of Ho et al. (2007), proposing matching as an non-parametric preprocessing procedure reducing the dependence of subsequent parametric models on specific distributional assumptions and improving the validity of causal inferences. This procedure effectively allows researchers to use the same parametric analyses following matching as would be done without matching. Accordingly, parametric estimation-based regression models were run as normal, while both paired and independent-samples tests are presented for comparisons of means between the age groups, taking into consideration the recommendation by Austin (2011) of treating paired samples as dependent data.

A mixed linear model with OA and matched YA was used to assess a three-way interaction between subjective acute psychedelic effects, age group, and changes in WEMWBS, aiming to expose age-related differences in salutogenic mechanisms. Pseudo-standardised regression coefficients β were calculated for this model to facilitate interpretability of the findings with $\beta < 0.2$ considered weak, $0.2 < \beta < 0.5$ moderate, and $\beta > 0.5$ as strong effects. Additional pairwise Pearson's correlations between WEMWBS change scores from baseline to the two- and four-week endpoint and subjective acute and post-acute psychedelic effects scores were calculated separately for OA and YA, with the purpose to illustrate three-way interaction results in a simplified manner. A significance level of $p < .05$ was applied to all statistical tests. Where applicable in case of multiple comparisons, both uncorrected and Bonferroni-corrected levels of significance are reported.

Prediction of changes in beliefs based on communitas A longitudinal exploratory path analysis was performed to determine the psychological mechanisms associated with changes in NPB. Included were items and scales pertaining to the acute subjective effects of the psychedelic as well as environmental and social contextual variables relevant to the retreat experience. Specifically, the intensity of mystical-type experience (MEQ) and communitas (COMS), measured on the day post-session, were expected to predict baseline-corrected NPB scores 4 weeks post-session, although due to non-significance of effects, only the COMS was retained in the model. This effect was hypothesized to be moderated by peer conformity measured at baseline, calculated as the sum of the four peer conformity-items from the short suggestibility scale. Demographic variables, trait absorption (MODTAS), baseline supernatural NPB, and alignment with the group assessed hours before the session via the IFS were included in the model as predictors of acute experience (MEQ and COMS) scores. Whenever a respondent attended more than one psychedelic ceremony and provided multiple reports, only the highest score for each of these scales was considered.

4.3 Results

4.3.1 Demographic Information

At the time of analysis, data was collected from a total of N = 886 participants. Individual surveys were completed by $N_{1\ (Baseline)} = 819$; $N_{2\ (Pre\text{-}session)} = 582$; $N_{3\ (post\text{-}session)} = 533$; $N_{4\ (post\text{-}retreat)} = 432$; $N_{5\ (4\text{-}week\ endpoint)} = 399$ participants. Details on the retreat duration, number of planned ceremonies, and substances used are shown in Table 4.1. Psilocybin mushrooms / truffles (80.0%) and ayahuasca (15.9%) jointly accounted for 95.9% of the substances that participants were planning to use during their experience, as indicated at baseline.

Table 4.1 Retreat Details Collected at Baseline.

Substance used	Psilocybin / Magic mushrooms / truffles	656 (80.0%)
	Ayahuasca	130 (15.9%)
	Other substance	33 (4%)
Retreat duration	1 day	279 (34.0%)
	2 days	20 (2.4%)
	3 days	154 (18.8%)
	4 – 6 days	200 (24.4%)
	7 days	180 (22.0%)
	8 or more days	46 (5.6%)
Psychedelic sessions	1 session	466 (56.9%)
	2 sessions	109 (13.3%)
	3 sessions	199 (24.2%)
	4 or more sessions	45 (5.5%)

Note. Absolute frequencies including corresponding percentages (in brackets) are presented.

Demographic information, including age, gender, nationality, education, employment, and marital status, median household income, as well as psychedelic use and psychiatric history collected in the baseline survey are presented in table 4.2. Most participants were white (90.7%), male (55.6%), and had some level of higher education (84.2%); the mean age of the sample was 44.4 years (SD = 12.6). Despite this relatively high mean age, a surprisingly large proportion of the sample had never used any psychedelic substances before (40.3%). Close to one third of the sample (32.0%) reported a lifetime psychiatric diagnosis, with depressive (17.9%) and anxiety disorders (16.9%) being the most common.

Table 4.2 Demographic Information Collected at Baseline.

Total N		**819**
Age (Mean ± SD)		44.4 ± 12.6
Gender	Female	359 (43.8%)
	Male	455 (55.6%)
	Other	5 (0.6%)
Nationality	United States	359 (43.8%)
	United Kingdom	160 (19.5%)
	Australia	31 (3.8%)
	Germany	28 (3.4%)
	Other countries (53 in total)	215 (26.3%)
Education	None	6 (0.7%)
	High School or equivalent (GED)	62 (7.6%)
	Associate / Technical Degree	58 (7.1%)
	College Diploma	250 (30.1%)
	Master's Degree	275 (33.6%)
	Doctorate or Professional Degree	168 (20.5%)
Employment	Student	46 (5.6%)
	Working full-time	520 (63.4%)
	Working part-time	120 (14.7%)
	Retired	73 (8.9%)
	Unemployed	60 (7.3%)
Median household income		9000 $ / month
Ethnicity	White	743 (90.7%)
	Black or African American	12 (1.5%)
	Asian	48 (5.9%)
	American Indian or Alaska native	3 (0.4%)
	Unknown / Prefer not to say	11 (1.3%) / 23 (2.8%)
Marital status	Cohabiting with partner	101 (12.3%)
	Married	340 (41.5%)
	Divorced	86 (10.5%)
	Separated	29 (3.5%)
	Never married	254 (31.0%)
	Widowed	9 (1.1%)
Psychiatric history	Depression	159 (17.9%)
	Anxiety	150 (16.9%)
	ADHD	57 (6.4%)
	Eating disorder	35 (4.0%)
	Alcohol dependence	18 (2.0%)
	Substance use disorder	13 (1.5%)
	Personality disorder	13 (1.5%)
	Obsessive compulsive disorder	11 (1.2%)
	Bipolar disorder	10 (1.1%)
	Psychotic disorder	9 (1.0%)
Previous psychedelic use	Never	330 (40.3%)
	Once	95 (11.2%)
	2-5 times	166 (20.3%)
	6-10 times	73 (8.9%)
	11-20 times	76 (9.3%)
	21-50 times	49 (6.0%)
	> 50 times	30 (3.7%)

Note. Absolute frequencies including corresponding percentages (in brackets) are presented.

4.3.2 Psychometric Properties of the Communitas Scale

To first validate our adapted measure of communitas in the context of psychedelic experiences, the Communitas Scale (COMS), we carried out a dimensionality assessment and confirmatory factor analysis, followed by correlational analyses to establish convergent and divergent (i.e. discriminant) construct validity.

Internal consistency. All considered approaches to determine the optimal number of factors to retain from the COMS indicated a unifactorial solution across the 8 items (Supplementary Figure A4.1) to be optimal, with an eigenvalue of 5.23 for the first factor which explained 65.7% of total variance in the data. Internal consistency of this single factor solution was excellent with Cronbach's alpha = 0.92. As shown in Figure 4.2, single-factor confirmatory factor analysis revealed that the standardised factor loadings for all items were above the recommended threshold of 0.5 for acceptable construct indicators (Hair et al., 2010), ranging from 0.588 (COMS6: "*I felt that social status became irrelevant*") to 0.930 (COMS2: "*I felt a sense of belonging with the other participants*"). Internal consistency was further demonstrated by good Composite Reliability (CR = 0.84) and Average Variance Extracted (AVE = 0.63) across the COMS items. The mean total communitas score (calculated as the sum across the 8 items) was 39.58 (SD = 11.23), corresponding to approximately 71% of the maximum score of 56.

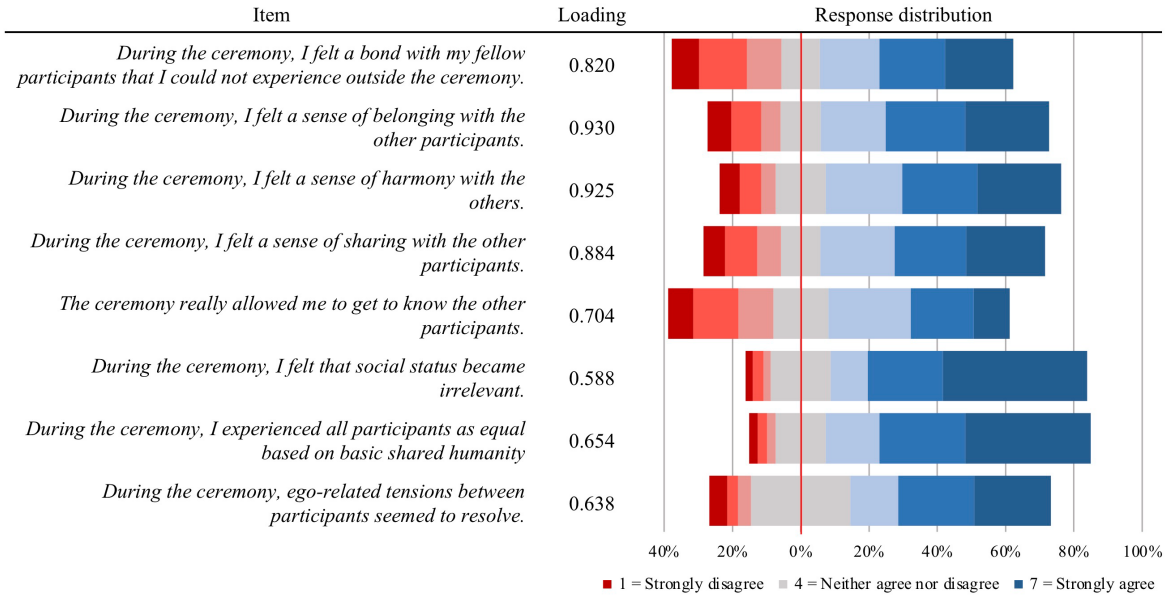


Figure 4.2 Items, Factor Loadings, and Response Distributions of the Communitas Scale (COMS). Loadings refer to standardized factor loadings based on a single-factor confirmatory factor analysis. This figure has been reproduced with permission from Kettner et al. (2021).

Construct validity. To assess convergent validity, bivariate Pearson correlations were calculated between COMS scores and the total as well as subscale-scores of validated subjective experience measures taken after each ceremony (IFS, PESC, MEQ, CEQ, ASC-VE; N in analysis = 720 observations). The results are displayed as a correlation heatmap in Figure 4.3. Convergent and discriminant validity of the COMS was established against the other subjective experience measures and their subscales following the Fornell & Larcker (1981) criterion: namely, that the square root of the COMS' average variance extracted ($\sqrt{AVE} = 0.79$) was larger than the inter-construct correlation between the COMS and any of the other considered measures. This criterion was met without exception, although strong convergence was nonetheless found between the COMS and two other measures of collective experience, i.e. identity fusion (IFS, r = .71) and perceived emotional synchrony (PESC, r = .76), as expected. Moderate to strong positive correlations were also found between the COMS and the MEQ (r = .60), especially for the 'Mystical' (r = .61) and 'Positive' (r = .56) subscales. The COMS was furthermore positively correlated with emotional breakthrough experiences (EBI,

r = .45) and visual aspects of the experience (ASC-Total), although to a lesser degree (r = .39). Lastly, weak negative correlations were discovered between the COMS and the 'Isolation' and 'Paranoia' subscales of the CEQ (r = -.30 and r = -.25, respectively).

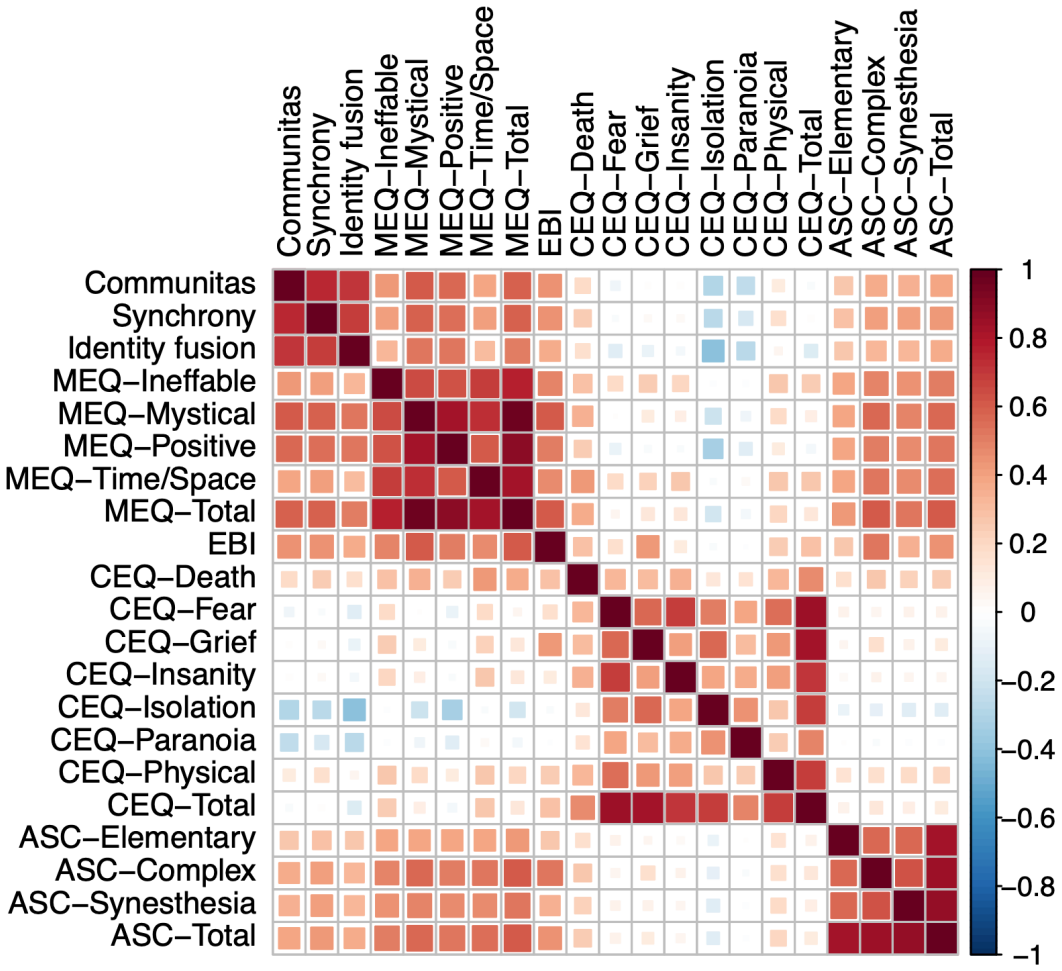


Figure 4.3 Correlation Heatmap of Subjective Experience Measures taken on the day after N = 720 psychedelic group sessions. Colour intensity and square sizes are both proportional to the (Pearson) correlation value. EBI: Emotional Breakthrough Inventory; MEQ: Mystical Experience Questionnaire; CEQ: Challenging Experience Questionnaire; ASC: Visual experience subscales of the Altered States of Consciousness Questionnaire. This figure has been adapted from Kettner et al. (2021).

The correlation between COMS scores and two additional Likert-scale items assessing perceived connection to 1) a facilitator and 2) another participant during the session were strong, with a Spearman correlation of r = 0.60 ($p < .0001$), and r = 0.67 ($p < .0001$), respectively (Figure 4.4).

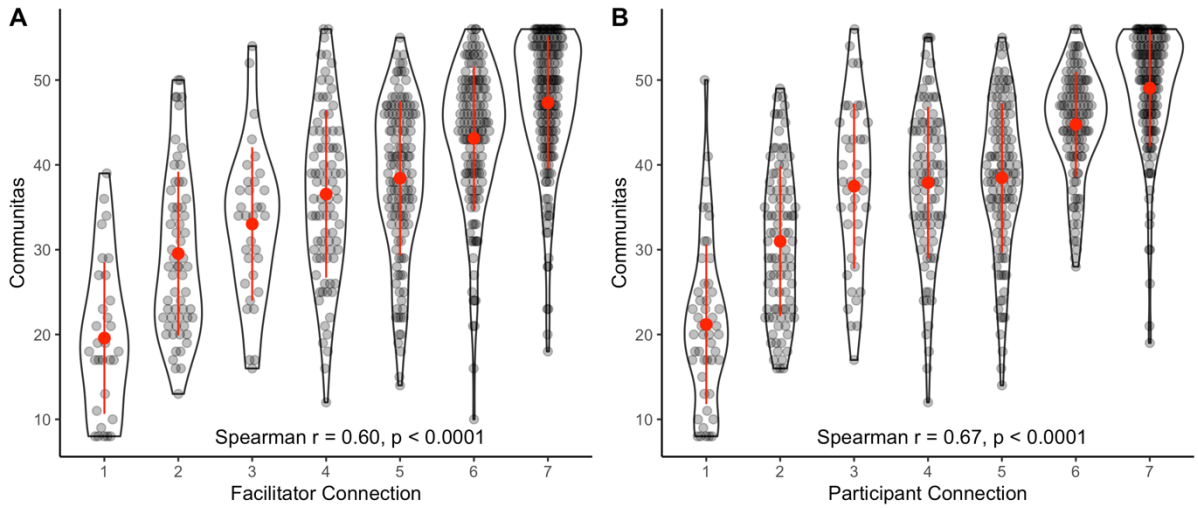


Figure 4.4 Distribution of Communitas Scores across Felt Connection with Others, including Likert-type responses of connection with a facilitator (A) or another participant (B) present during the psychedelic session. This figure has been reproduced with permission from Kettner et al., (2021).

4.3.3 Changes in Primary Outcomes Predicted by Communitas

To ascertain the predictive (i.e. criterion validity) of the COMS, correlations were calculated between COMS scores taken on the day after psychedelic group sessions and prospective changes in primary and secondary outcomes from baseline to 4 weeks post-session. Two-sided paired t-tests showed that social connectedness (SCS, M = 36.3, SD = 10.1), well-being (WEMWBS, M = 51.2, SD = 9.2), and general connectedness (WCS, M = 68.5, SD = 19.1) were significantly higher at the 4-week endpoint than at baseline (Figure 4.5A-C, M = 31.5, SD = 11.1, t(373) = -9.9, p < .0001; M = 45.5, SD = 8.8, t(377) = -12.9, p < .0001; M = 54.2, SD = 19.0, t(377) = -15.7, p < .0001; respectively), with substantial increases of medium and large effect sizes (Cohens d = 0.46, 0.62, 0.75 for SCS, WEMWBS, and WCS). Changes in well-being, social, and general connectedness were significantly, albeit weakly, correlated with COMS scores experienced during the psychedelic session (Figure 4.5D-F; r = .22, r = .25, r = .31, respectively).

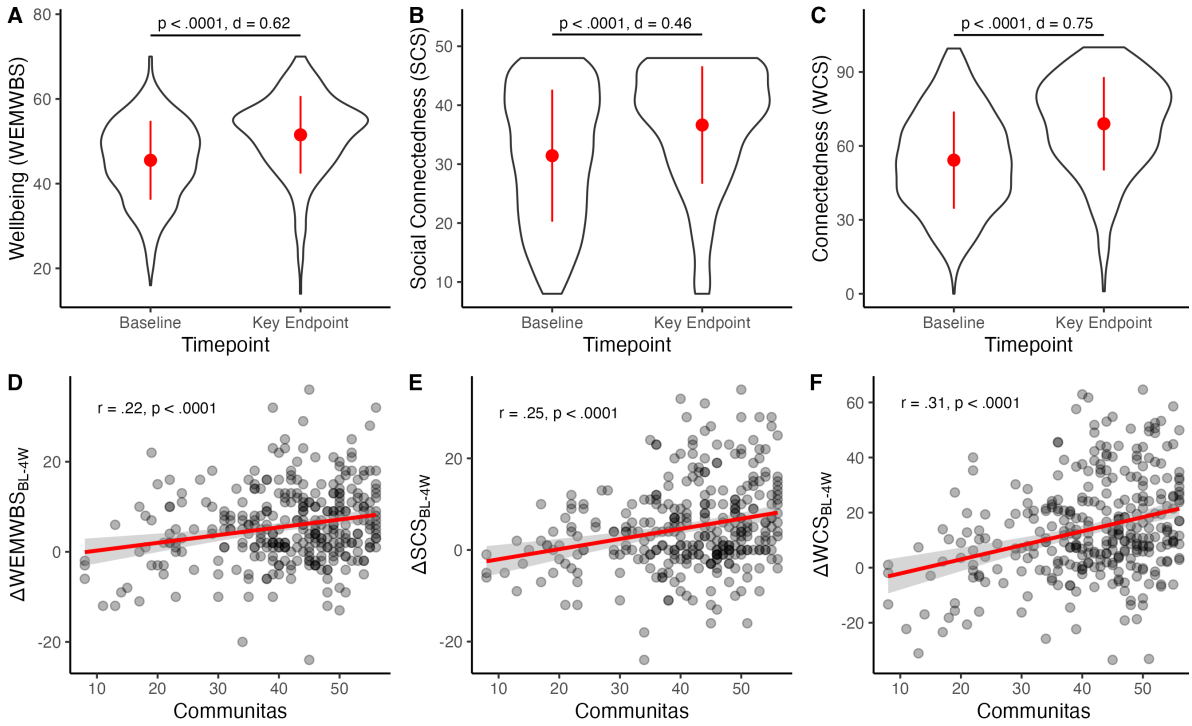


Figure 4.5 Post-psychedelic Increases in Psychological Well-being and Connectedness Positively Correlate with Communitas experienced during psychedelic group sessions (D-F). Panels A-C show changes in well-being (A), social connectedness (B), and general connectedness (C) from 2 weeks before to 4 weeks after participation in a psychedelic group session or retreat. Red dots and lines represent mean ± SD (A-C) and trend lines (D-F). SCS: Social Connectedness Scale, WCS: Watts Connectedness Scale, WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

4.3.4 Secondary Outcomes

All secondary outcome variables changed significantly between baseline and key endpoint (see Table 4.3) with negligible (interpersonal tolerance, d = 0.19) to large (depressive symptoms, d = -0.60) effect sizes. Further establishing the predictive validity of the COMS, communitas experienced during the psychedelic session was significantly, although weakly, correlated with changes on several of the secondary outcomes, including interpersonal tolerance (IPTS, r = .19), trait-anxiety (STAI, r = -.16), and depressive severity (QIDS, r = -.11).

Table 4.3 Changes on Secondary Outcomes and Associations with Communitas

	Baseline (N = 819)		Key Endpoint (N = 399)					Change scores vs Communitas	
	M	SD	M	SD	*t*	*p*	*d*	*r*	*p*
QIDS	6.98	4.77	4.20	3.33	-11.015	<.0001	-.60	- .11	.04
STAI	13.53	4.27	11.13	3.65	-11.745	<.0001	-.53	-.16	<.01
IPTS	5.57	0.74	5.69	0.68	5.043	<.0001	.19	.19	<.001

Note. Means (M) and standard deviation (SD) are reported for each outcome at baseline (2 weeks before) and key endpoint (4 weeks after) a psychedelic retreat or ceremony. Significance and Cohen's d effect sizes are reported for two-sided pairwise t-tests, as well as correlation coefficients with Communitas experienced during the psychedelic sessions. QIDS: Quick Inventory of Depressive Symptomatology; STAI: Trait version of the State-Trait Anxiety Inventory; IPTS: warm tolerance subscale of the Interpersonal Tolerance Scale;

4.3.5 Path Modelling

An initial longitudinal path model exploring the causal role of communitas within psychedelic retreats was fitted including regression paths between variables from a total of five time points (Figure 4.1). Listwise deletion showed better model fit than maximum-likelihood imputation of missing data, thus, N=213 subjects who completed all five time points were included in the analysis.

The initial model demonstrated less than acceptable fit on two of the four fit indices, namely the RMSEA and SRMR. During the model pruning process, several variables were iteratively dropped due to lack of direct or mediated effects on communitas (COMS) or either of the outcomes SCS and WEMWBS: Identity Fusion (IFS) measured before and after the ceremony, as well as after the retreat; Perceived emotional synchrony (PESC); Age. The final model exhibited good fit on all indices except the SRMR, where it nevertheless reached an acceptable fit (Table 4.4).

Table 4.4 Recommended and Actual Fit Indices for Pruned Path Models

	Recommended fit		Actual fit		
Fit index	Acceptable fit	Good fit	COMS	EBI	MEQ
CFI	> .90	> .95	.984	.945	.959
χ^2/df	< 3.0	< 2.0	1.25	2.00	1.81
RMSEA	< 0.08	< 0.05	.039	.079	.065
SRMR	< 0.08	< 0.05	.057	.082	.069

Note. CFI: Comparative Fit Index, χ2: Chi-square test statistic, df: degrees of freedom, RMSEA: Root Mean Square Error of Approximation, SRMR: Standardized Root Mean Square Residual

In the final model (Figure 4.6), retreat communitas (i.e. communitas reported in reference to the retreat as a whole, rather than a specific ceremony), significantly predicted well-being and social connectedness 4 weeks later, with weak to moderate effect sizes ($\beta = 0.16$, $p < .01$ and $\beta = 0.19$, $p < .001$, respectively). Retreat communitas was, in turn, significantly predicted by communitas experienced acutely during the ceremony, both directly ($\beta = 0.41$, $p < .0001$), and indirectly mediated by self-disclosure over the course of the retreat ($\beta = 0.18*0.34 = 0.06$, $p < .05$). Ceremony communitas was influenced most strongly by rapport with facilitators and participants, assessed hours pre-ceremony, both directly ($\beta = 0.19$, $p < .01$) and indirectly mediated by perceived emotional support during the ceremony ($\beta = 0.36 * 0.38 = 0.14$, $p < .001$). Trait absorption measured at baseline positively predicted ceremony communitas ($\beta = 0.17$, $p < .01$), while female gender was negatively associated with communitas ($\beta = -0.17$, $p < .01$). The standardised covariance between psychological well-being and social connectedness at the 4-week key endpoint was large ($r = .65$, $p < .0001$).

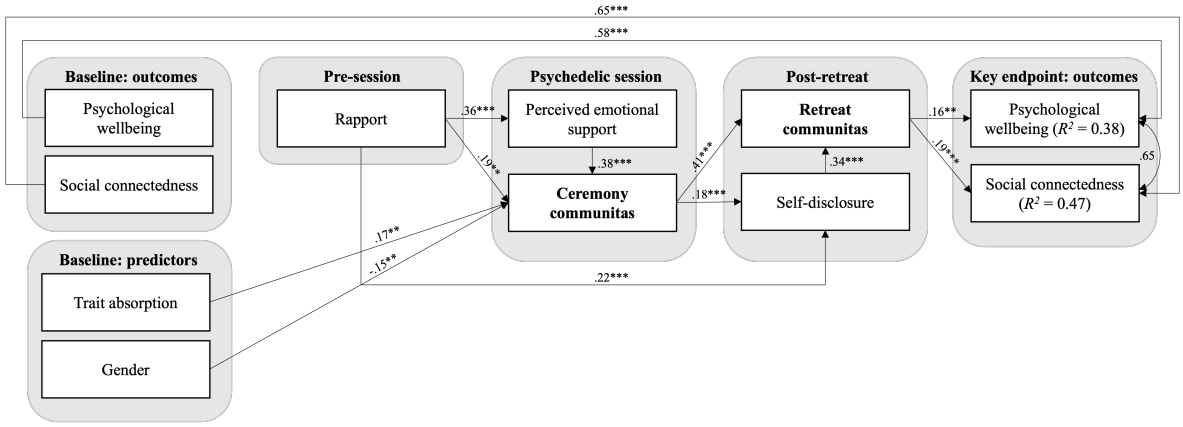


Figure 4.6 Final Path Model Showing Psychosocial Mechanisms of Psychedelic Retreats, measured across 5 time points. Standardized coefficients are shown for significant ($p < .05$) regression paths. This figure has been reproduced with permission from Kettner et al. (2021).

* indicates $p < .05$, ** $p < .01$, *** $p < .001$

To ascertain the relative influence of the classically studied intrasubjective, as opposed to intersubjective psychological mechanisms at play during psychedelic retreats, two additional path models were pruned that contained scores on the emotional breakthrough inventory (EBI, Figure 4.7A) and mystical experience questionnaire (MEQ, Figure 4.7B) instead of communitas experienced during ceremony. While absorption remained a significant predictor of EBI ($\beta = 0.15$, $p < .05$) and MEQ ($\beta = 0.30$, $p < .0001$) scores, neither were affected by gender, which was thus dropped from both models. In line with the COMS model, both MEQ and EBI were higher for subjects that felt emotionally supported during the session ($\beta = 0.34$, $p < .0001$ and $\beta = 0.27$, $p < .0001$, respectively), and both EBI ($\beta = 0.18$, $p < .0001$) and MEQ ($\beta = 0.26$, $p < .0001$) were associated with greater self-disclosure post-session. The most salient difference exhibited by these two additional models when compared to the COMS model, however, was the preservation of direct paths from both MEQ and EBI to the primary study outcomes, indicating that not all their effects were explained by mediation through self-disclosure and retreat communitas. Specifically, the EBI had a significant direct effect both on well-being ($\beta = 0.19$, $p = 0.002$) and social connectedness ($\beta = 0.18$, $p = 0.002$), while the MEQ retained a weak, yet significant direct effect on social connectedness ($\beta = 0.09$, $p = 0.047$). Of

all three models, the greatest amount of variance in the primary outcomes was explained by the EBI model (43% of well-being, 50% social connectedness at the key endpoint), while the COMS model explained least (38% and 47%, respectively), despite being the best fitting model (Table 4.4).

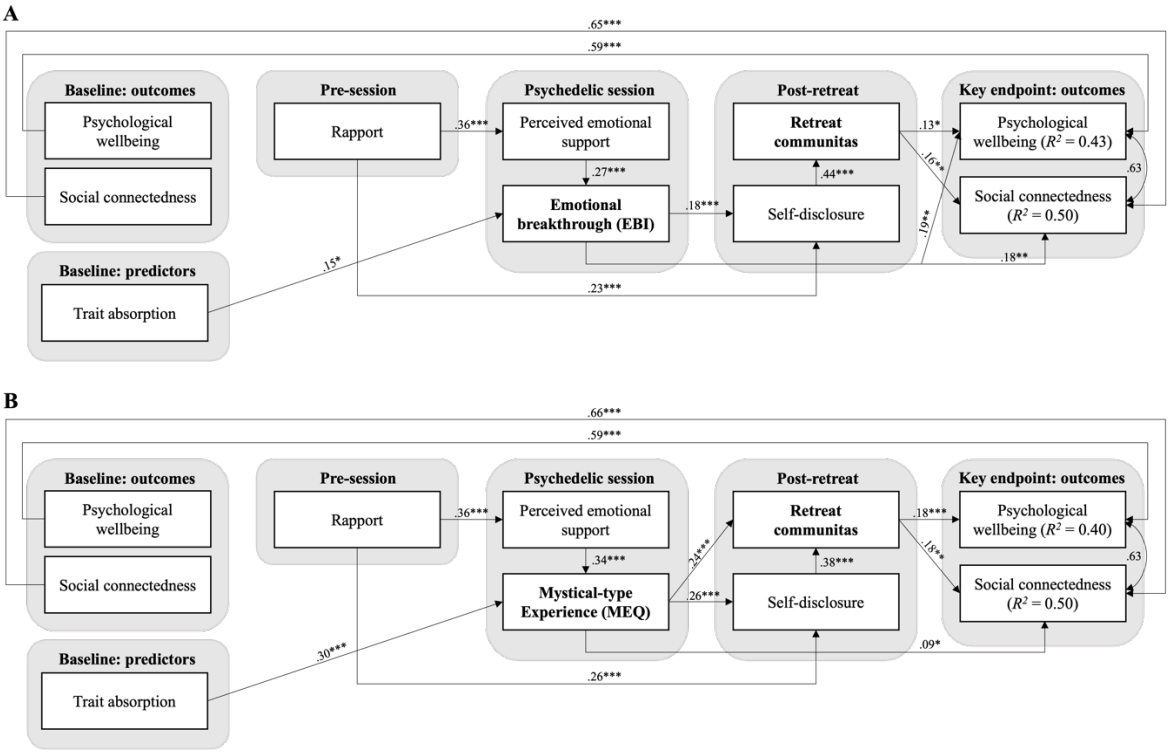


Figure 4.7 Additional Path Models Showing the Interaction of Emotional Breakthrough and Mystical-type Experiences With Psychosocial Dynamics of psychedelic retreats. Standardized coefficients are shown for significant ($p < .05$) regression paths. EBI: Emotional Breakthrough Inventory; MEQ: Mystical Experience Questionnaire

* $p < .05$, ** $p < .01$, *** $p < .001$

4.3.6 Communitas in Older Adults

Both naturalistic studies and clinical trials involving psychedelics tend to be biased towards younger demographics. The observation that the participants recruited for this study exhibited a relatively high mean age of 44 (Table 4.2), prompted us to perform post-hoc analyses focusing specifically on older adults (OA) that participated in this study, published in full in Kettner et al., (2024). Among 106 participants who reported ≥60 years of age, 62 had

completed the baseline as well as the 24 h post-session survey, yielding the final OA sample analysed in this post-hoc analysis.

Table 4.5 Demographic Characteristics of the Older Adult Subsample and Matched Younger Adults

	OA (N=62)	YA matched (N=62)
Age		
Mean (SD)	65.1 (4.02)	46.5 (10.0)
Median [Min, Max]	64.0 [60.0, 75.0]	49.0 [24.0, 59.0]
Gender		
Male	31 (50.0%)	31 (50.0%)
Female	31 (50.0%)	31 (50.0%)
Other	-	-
Education/degrees		
None	1 (1.6%)	0 (0%)
High school	3 (4.8%)	2 (3.2%)
Technical degree	4 (6.5%)	5 (8.1%)
College diploma	11 (17.7%)	18 (29.0%)
Master	19 (30.6%)	30 (48.4%)
PhD/MD/Law degree	24 (38.7%)	7 (11.3%)
Psychiatric diagnoses		
Yes	16 (25.8%)	15 (24.2%)
No	46 (74.2%)	47 (75.8%)
Previous psychedelic use		
Never	35 (56.5%)	28 (45.2%)
1-5 times	15 (24.2%)	10 (16.1%)
> 5 times	12 (29.3%)	24 (38.7%)
WEMWBS at baseline		
Mean (SD)	48.5 (7.79)	48.8 (9.79)
Median [Min, Max]	50.0 [31.0, 63.0]	50.5 [20.0, 70.0]
Psychedelic dose		
Mean (SD)	2.10 (0.646)	2.13 (0.586)
Median [Min, Max]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]

Note. OA: Older adults; SD: Standard Deviation; WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale; YA: Younger adults

Among these 62 OA, 53 completed the post-retreat questionnaire, evaluating experiences across the entire retreat period; 44 completed the two-week, 61 completed the four-week, and 23 completed the six-month endpoint. From a total of 430 younger adults (YA) with age <60 years who completed at least the baseline and the 24 h post-session survey, a set of 62 matched YA was selected using nearest k-neighbour matching (Table 4.5).

The mean age in the identified 62 OA was 65.1 years (SD=4.02; range = 60-75) and exactly half (31/62, 50.0%) were male. A majority (43/62, 68.5%) of OA had a Master's degree or higher, no history of diagnosed mental illness (46/62, 74.2%), and no prior experiences with psychedelics (35/62, 56.5%). Among OA who indicated psychiatric diagnoses, the most common were major depressive disorder (10/16) and anxiety disorder (9/16); alcohol dependence and ADHD were indicated by two individuals, respectively; personality, bipolar, and eating disorders by one person each. 59 OA attended psilocybin mushroom or truffle sessions (57 of which took place at retreat centres in the Netherlands or Jamaica), while three individuals indicated ayahuasca as the psychedelic used. A sample of 62 YA (mean age in years [SD] = 46.5 (10); range = 24–59) was selected via nearest k-neighbour matching for comparison purposes.

We explored whether age-group-dependent acute and post-acute subjective psychedelic effects predicted long-term well-being outcomes via a mixed effects linear regression model including three-way interaction terms between age group, time, and each acute predictor variable. To prevent multicollinearity issues, variance inflation factors (VIF) for each included predictor variable were calculated, resulting in the removal of the MEQ from the model (VIF = 3.7) based on the generally accepted VIF cut-off of 2.5 (Johnston et al., 2018). After excluding MEQ, the highest VIF was below the established cut-off (VIF = 2.1), found for the

EBI. The resulting model revealed a significant and large negative three-way interaction between EBI, older age group, and post-psychedelic endpoints at two- (β = -0.78, 95% CI [-1.43, -0.13], p = .02) and four-weeks (β = -0.80, 95% CI [-1.46, -0.15], p = .02), indicating that emotional breakthrough experiences contributed less to improved well-being in OA compared to YA. Furthermore, a very large, albeit only marginally significant positive three-way interaction was detected for post-retreat COMS scores, OA, and the four-week end-point, suggesting that relational experiences of sharing and togetherness across the retreat may have played a larger role for predicting improved well-being in OA when compared to YA (β = 2.04, 95% CI [-0.21, 4.28], p = .08).

Table 4.6 Differential Salutogenic Mechanisms for Older and Younger Adults Indicated by Three-way Interactions from a Mixed Linear Regression Model (N=82)

Fixed effects				
Term	β	SE	t-value	p
EDI:Age 60+:2-week endpoint	0.05	0.21	0.25	.80
EDI:Age 60+:4-week endpoint	0.05	0.24	0.217	.83
EBI:Age 60+:2-week endpoint	-0.78	0.33	-2.354	**.02**
EBI:Age 60+:4-week endpoint	-0.8	0.33	-2.416	**.02**
CEQ:Age 60+:2-week endpoint	0.18	0.23	0.788	.43
CEQ:Age 60+:4-week endpoint	0.2	0.23	0.855	.39
COMS:Age 60+:2-week endpoint	0.38	0.53	0.727	.47
COMS:Age 60+:4-week endpoint	-0.14	0.58	-0.24	.81
$COMS_{PR}$:Age 60+:2-week endpoint	-0.04	1.05	-0.04	.97
$COMS_{PR}$:Age 60+:4-week endpoint	2.04	1.15	1.793	*.08*
PIS:Age 60+:2-week endpoint	-0.06	0.39	-0.16	.87
PIS:Age 60+:4-week endpoint	-0.09	0.38	-0.234	.82

Random effects		
	V	SD
Participant (intercept)	36.74	6.062

Model fit		
	Marginal	Conditional
R^2	26.9%	70.0%

Note. Pseudo-standardized regression coefficients (β). CEQ: Challenging Experience Questionnaire; COMS: Communitas Scale; EBI: Emotional Breakthrough Inventory; EDI: Ego-Dissolution Inventory; PR: Post-retreat; PIS: Psychological Insight Scale; SD: Standard Deviation; SE: Standard Error; V: Variance

Correlation analyses between predictors and well-being change scores (Figure 4.8) in this matched subsample of OA and YA further illustrate these relationships: EBI was moderately associated with well-being change scores at four-weeks in YA (r = .43, p = .008), but only negligibly in OA (r = -.04, p = .79), while COMS-PR was positively associated with well-being change scores at four-weeks in OA (r = .37, p = .03) but not in YA (r = .01, p = .94). Interestingly, none of the other acute and post-acute variables that significantly correlated with well-being changes in YA were shown to significantly correlate with well-being changes in OA. Together, these findings suggest that therapeutic mechanisms underlying psychedelic experiences may fundamentally differ between OA and YA, indicating a unique role for psychosocial experiences in the older group.

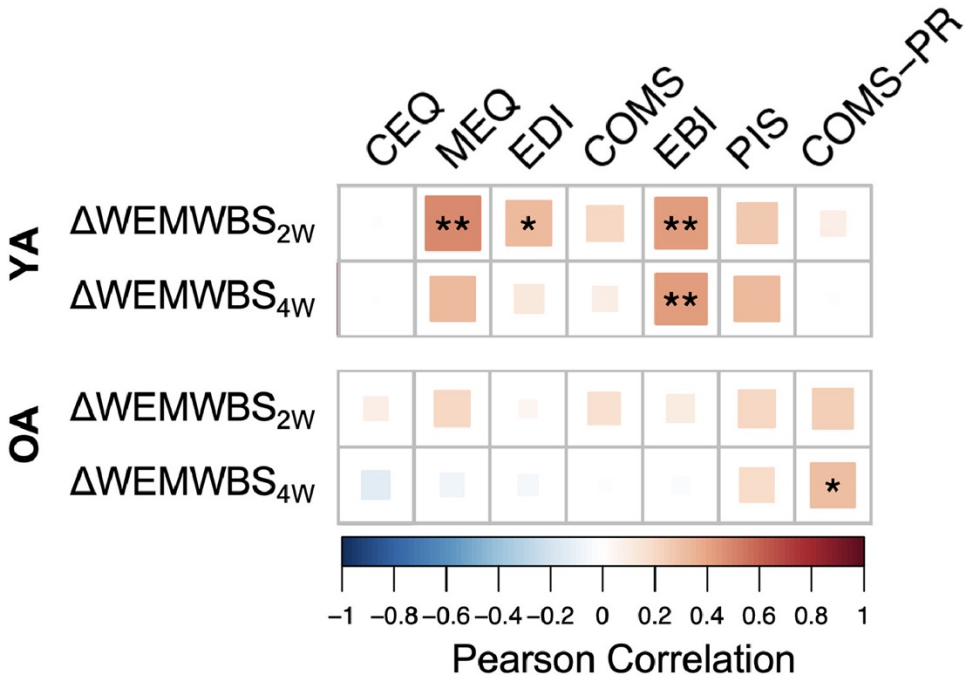


Figure 4.8 Pearson Correlation Heatmap Showing Associations Between Subjective Psychedelic Effects and Changes in Well-being from baseline to two weeks (2W) and four weeks (4W) after a psychedelic group session in subsamples of 62 older adults (OA) and baseline-matched younger adults (YA). This figure has been reproduced with permission from Kettner et al. (2024). CEQ: Challenging Experience Questionnaire; COMS: Communitas Scale; EBI: Emotional Breakthrough Inventory; EDI: Ego-Dissolution Inventory; MEQ: Mystical Experience Questionnaire; PR: Post-retreat

*p < .05; **p < .01.

4.3.7 Communitas Mediates Changes in Metaphysical Beliefs

A longitudinal exploratory path analysis was performed to examine mechanisms associated with shifts in the relevant non-physicalist beliefs. Included in the model were items and scales pertaining to the acute subjective effects of psychedelics as well as environmental and social-contextual variables relevant to the retreat experience. Results supported a model with excellent fit (Table 4.7) in which communitas ($\beta = 0.24$, $p < .0001$) - moderated at trend level by baseline scores of peer conformity ($\beta = 0.07$, $p = .075$) - predicted subsequent changes in the NPB factor (Figure 4.9). Acute communitas was itself predicted by higher trait absorption ($\beta = 0.16$, $p = .017$), male gender ($\beta = -0.15$, $p = .019$), younger age ($\beta = -0.14$, $p = .015$), baseline NPB ($\beta = 0.16$, $p = .024$), plus identity fusion (i.e. identification with the retreat group) assessed shortly prior to the experience ($\beta = 0.20$, $p < .01$), partially replicating the results obtained in the path model predicting changes in well-being and social connectedness (Figure 4.6).

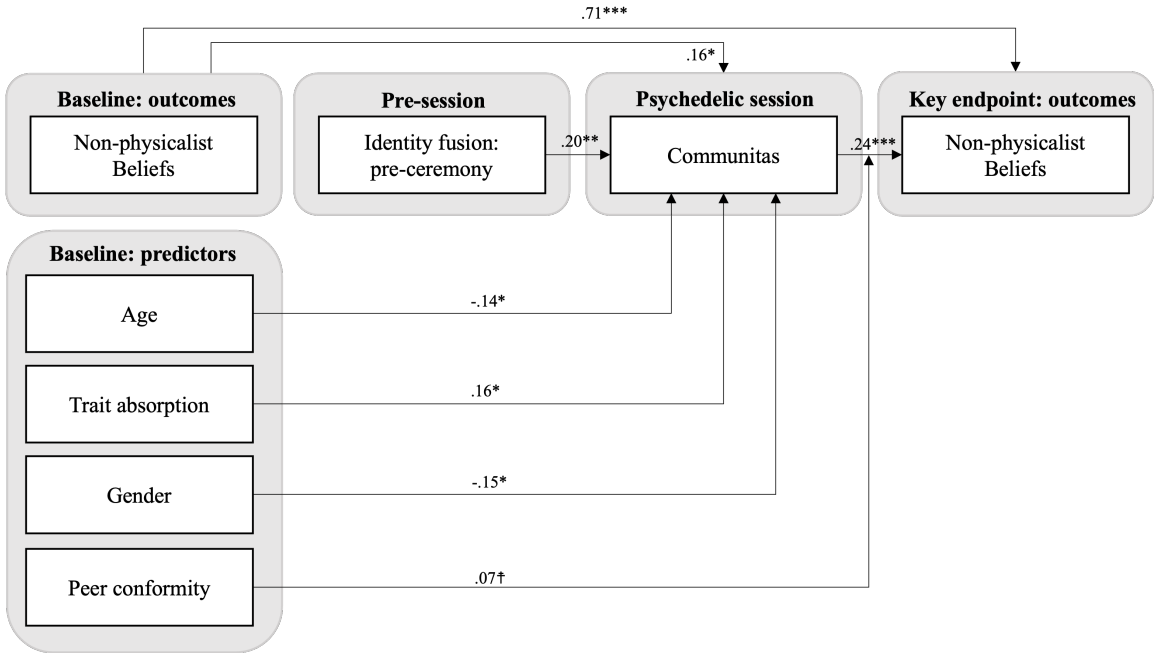


Figure 4.9 Path Model Showing Psychosocial Mechanisms Underlying Changes in Metaphysical Beliefs following psychedelic retreats. Standardized coefficients are shown for trend-level significant ($p < .10$) regression paths.

† indicates $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.7 Recommended and Actual Fit Indices for Path Model Predicting Non-Physicalist Beliefs

Fit index	Final model	Good fit	Acceptable fit
CFI	1.000	> .95	> .90
χ^2 /df	0.67	< 2.0	< 3.0
RMSEA	.000	< 0.05	< 0.08
SRMR	.027	< 0.05	< 0.08

Note. CFI: Comparative Fit Index, χ2: Chi-square test statistic, df: degrees of freedom, RMSEA: Root Mean Square Error of Approximation, SRMR: Standardized Root Mean Square Residual

4.4 Discussion

More so than with conventional psychopharmacological interventions, outcomes of psychedelic treatments are known to crucially depend on the acute subjective effects experienced by the user, which, in turn, are affected by the psychological and environmental context of their use (Carhart-Harris, Roseman, et al., 2018). Yet, the nature of modern testing environments has so far hindered the quantitative study of what constitutes one of the most ubiquitous characteristics of naturalistic psychedelic use, i.e. the experience of psychedelic states as a collective activity. The present study constitutes a first step toward the quantitative assessment of psychosocial effects in guided psychedelic group experiences, enabled by the collection of the largest prospective sample of psychedelic use published to date. By analysing data from 720 individual psychedelic ceremony experiences reported by 886 participants assessed across 5 time points, we validated a novel measure of communitas—an intense sense of togetherness and shared humanity—and clarified its relationships with existing measures of intra- and intersubjective phenomenology. Importantly, communitas was found to significantly predict enduring increases in psychological well-being and social connectedness following psychedelic use. Further examining the contextual determinants and downstream effects of communitas, a longitudinal path analysis revealed several psychosocial 'set and setting' predictors of communitas, as well as a mediating role of self-disclosure in extending communitas beyond the acute effects experienced during the psychedelic session.

In line with previous research using a similar measure of communitas in the context of nightclubbing (Taheri et al., 2016), good internal consistency, composite reliability, and convergent validity were established for communitas in the context of psychedelic group experiences. Confirming the conceptual link between the constructs, communitas was strongly associated with both perceived emotional synchrony and identity fusion, while still distinct enough to establish discriminant validity and thus demonstrate the new measure's additional value according to the Fornell and Larcker (1981) criterion. Perceived emotional synchrony, conceptually derived from Durkheim's (1912) notion of 'collective effervescence' - an important inspiration for Turner's (1969) model of communitas (Rose, 2025) - has similarly been shown to enhance collective identity, social cohesion, personal and collective self-esteem and efficacy, positive affect, positive social beliefs, compassion, and individual wellbeing during collective events such as folkloric festivals, protest demonstrations, mindful dancing, and sport activities (Páez et al., 2015; Pizarro et al., 2020; Wlodarczyk et al., 2020).

Although closely related, operationalisations of collective effervescence, synchrony, and similar social psychological constructs such as identity fusion, group cohesion or social bonding, differ from communitas in that they typically capture affective arousal, behavioural alignment, or perceived closeness within existing social structures, whereas communitas refers to a transient, liminal state of equality and shared humanity that momentarily transcends ordinary social roles and hierarchies. As such, communitas, more so than its conceptual neighbours, can be understood as a collective analogue to the experience of psychedelic ego-dissolution, known to be positively associated with long-term outcomes of psychedelic use (Kałużna et al., 2022). In a similar vein, the present study provides novel evidence of enduring prosocial and psychological benefits derived from the experience of communitas during a collective psychedelic experience. In particular, post-psychedelic improvements in wellbeing,

social connectedness, depressive symptoms, trait anxiety, and interpersonal tolerance, were found to be positively associated with the extent of communitas experienced during psychedelic ceremonies, demonstrating the predictive (criterion) validity of the here proposed instrument. This finding adds to quantitative studies on collective activities without a pharmacological component that have demonstrated a role of communitas in the formation of collective identity (Lee et al., 2015), experiential involvement (Taheri et al., 2016), volunteer engagement and commitment (Curran & Taheri, 2021), and repeat attendance of events (Jahn et al., 2018; Lee et al., 2015; McGinnis et al., 2012), but not yet shown any enduring improvements of psychological and social health.

The strongest association between any long-term outcome and communitas was observed for connectedness, pointing to the ability of positive relational experiences during psychedelic ceremonies to induce a sense of belongingness with oneself, others, and the world, beyond the context of the immediate social environment. Social connectedness is a well-established determinant of both mental and physical health (Alexander, 2000; Hari, 2020), with large-scale studies and meta-analyses reliably showing social isolation and loneliness to comparable to obesity and heavy smoking in their effects on mortality (Holt-Lunstad et al., 2010; Pantell et al., 2013; Rico-Uribe et al., 2018). The capacity of psychedelic use to enduringly enhance feelings of social connectedness has been shown in several other prospective studies, (Carhart-Harris, Erritzoe, et al., 2018; Weiss et al., 2021), including also collective festivals (Forstmann et al., 2020) and psychedelic retreats (Lowe et al., 2024). Further underlining the capacity of collective environments of guided psychedelic use to instil lasting positive psychosocial effects, the current sample showed increases in social connectedness that were on average 2.7 times higher than in a methodologically comparable

naturalistic study (ΔSCS = 4.8 vs. 1.8, as reported in Carhart-Harris, Erritzoe, et al., 2018) not limited to guided group settings.

While an extant body of research supports the mediating role of intrasubjective psychedelic effects for their long-term outcomes (Romeo et al., 2025), most of this research is based on clinical trials or prospective studies in psychedelic enthusiasts, both of which tend to be biased towards younger demographics (Bouchet et al., 2024). In this context, the absence of any significant correlations between acute psychedelic effects and long-term changes in older adults (OA) represents an interesting contradiction to previous work showing that the quality of the acute experience constitutes a key predictor of psychedelic-induced changes in well-being. In contrast, only the experience of communitas rated in reference to the entire retreat—not just the psychedelic session- was significantly associated with well-being changes in OA. The strong, albeit only marginally significant 3-way interaction including age group and retreat-communitas suggests that OA might benefit from psychedelics for different reasons than their younger counterparts, greater relevance being given to the experience of togetherness and social bonds that can occur in group settings than to the individual, intrapersonal experience. The witnessing of other participants' vulnerability and the resulting emotional intimacy generated through sharing rounds before and after dosing sessions might be particularly impactful to OA, for whom social contact, especially with nonfamily members, is known to decrease (Sander et al., 2017). Indeed, from the present data it is unclear to what extent the consumption of the psychedelic substance itself would even have been necessary for OA to experience the detected psychological benefits. Future research should thus further explore the details of psychotherapeutic and group activities taking place at psychedelic retreats, and their psychological benefits for participants, as well as the validity of instruments assessing the overall experience in OA. Conceivably, the psychedelic session itself could be

seen as a non-essential part, primarily providing the context for an intimate and intergenerational group-based intervention with the potential to tackle the negative emotional and cognitive health consequences of social isolation in the elderly (Krzeczkowska et al., 2021; Murayama et al., 2015)

While the present analyses focussed on the role of acute intersubjective psychedelic effects, additional path models including validated intrasubjective psychedelic effect measures, specifically mystical-type (MEQ) and emotional breakthrough experiences (EBI), revealed several mechanistic differences. While in both cases, effects on long-term outcomes were partially mediated through self-disclosure, significant direct effects from mystical-type and breakthrough experiences on well-being and social connectedness suggest that these experiences may, even in group settings, elicit psychological benefits through pathways independent of the psychosocial context. In the case of mystical-type experiences, one such factor has been discussed as enhancing connectedness to the self and to the world, the latter also including notions of spiritual well-being (Carhart-Harris, Erritzoe, et al., 2018). Additionally, psychological insight has recently been investigated as a mediating factor of psychedelic-induced improvements in well-being, where the insightfulness of the experience has been found to mediate the effects of mystical-type, and, even more so, emotional breakthrough experiences, on depression outcomes (Peill et al., 2022). Nevertheless, it is likely that within this framework too, psychosocial context is not without relevance, in that both the adoption of new spiritual frameworks and the acquisition of insights may be influenced by peers (or therapists/guides) who thereby contribute to the subject's integration of their psychedelic experiences (Bathje et al., 2022; Cheung et al., 2024; Gezon, 2024). This was partially demonstrated by the secondary finding that post-psychedelic changes in metaphysical beliefs were mediated by experiences of communitas, a result that corroborated prior analyses

in the same sample, showing a similar mediating role for emotional synchrony (Timmermann et al., 2021). Indeed, path analyses revealed that the effects of emotional breakthrough and mystical-type experiences on well-being and connectedness were at least partially mediated by self-disclosure and communitas across the retreat. Together, these findings expand current models that place individual experience as a central psychological mechanism for the attainment of mental health outcomes, by supporting the notion that experiencing these states with others may further enhance the therapeutic action of psychedelic substances.

The observed causal interdependence between inter- and intrasubjective effects in the discussed path models can be interpreted as an instantiation of the principle of circular causality put forth in enactive models of (social) cognition. Interpersonal factors such as pre-session rapport, identity fusion, and the experience of emotional support during sessions not only intensified experiences of communitas, but also emotional breakthrough, and the well-validated mystical-type experiences. An environment-person-environment feedback loop is continued in the finding that the long-term impact of these acute psychedelic effects on well-being and social connectedness was mediated by experiences of sharing and togetherness outside the immediate ceremony setting, across the retreat. In parallel to the evidence of bidirectional relationships between therapeutic alliance, acute psychedelic effects, and treatment outcomes observed in the previous chapter, there appears to be a dynamic interplay and mutually reinforcing relationship between relational factors and psychedelic drug effects also in group settings: experienced rapport and interpersonal support enhance the intensity of drug effects, which in turn foster greater sharing and a deepened sense of psychosocial belonging, ultimately contributing to positive outcomes for individual mental health.

Given the added monitoring challenges and regulatory hurdles of conducting group-based psychedelic sessions in a clinical context, future psychedelic trials might benefit from considering group-based preparation and integration activities, as was done e.g., by Anderson et al. (2020). Research has shown that attendance of psychedelic integration groups can be especially useful for attenuating potential negative responses (Modlin et al., 2024), which could represent a cost-effective, psychosocially enhanced method to mitigate adverse long-term responses to psychedelics. Importantly, institutional oversight would allow for more careful curation of such group environments, circumventing some of the ethical risks that have been outlined for community-based integration groups, such as violations of confidentiality or involuntary belief transmission (Cheung et al., 2024). Similar risks apply to group settings of psychedelic use, such as psychedelic retreats assessed for the present study. While the practice of mutual self-disclosure within sharing circles may ideally become a platform for participatory sense-making (De Jaegher & Di Paolo, 2007; Fuchs & De Jaegher, 2009), whereby meaning emerges through social interactions between dynamically autonomous agents, rather than being transmitted via a unidirectional sender-receiver model, epistemic risks are inherent to the state of psychedelic-enhanced suggestibility. For example, Dupuis (2021, 2022) provides detailed qualitative accounts of belief transmission in cases where interpretative authority over participants' experiences is claimed by a ritual leader figure. These cases show how interactions involving 'epistemic gaslighting' (Spear, 2023) and peer-pressure, can undermine participant autonomy by exploiting psychedelic-induced hypersuggestible states, in order to create targeted conversion experiences. While such strong ideological priors may be less prevalent in commercial, Westernized retreat settings, reports such as this illustrate that naturalistic group retreats, such as in the present study, ought not to be confused with clinically validated therapeutic interventions that involve careful screening, therapeutic support and long-term attendance to potential adverse events (Rucker & Young, 2021).

Limitations and future directions. The web-based observational design of the current study entailed several intrinsic limitations. Firstly, the lack of experimental control meant prevent confirming whether participants completed questionnaires at the correct time points in reference to their experience, and verifying under what conditions these measures were completed. Additionally, the substantial number of participants dropping out from the study before completing the key endpoint may have introduced a systematic attrition bias, although analyses in a similar sample suggest that predictors of attrition in observational psychedelic research may be no more problematic than in other fields of research (Hübner et al., 2021).

Moreover, the setting considered in this study attracted a predominantly WEIRD (white, educated, industrialized, rich, democratic) (Henrich et al., 2010), self-selected sample, reflecting a pervasive problem in psychedelic research (George et al., 2020), including also clinical trials (Hughes & Garcia-Romeu, 2024; Michaels et al., 2018). In the current case, self-selection biases were further accentuated by economic barriers to the participation in—often costly— psychedelic retreats. Consequently, the cross-cultural validity of the here proposed communitas scale remains unclear, if not doubtful, given the limited cultural translatability of abstract concepts such as 'ego', invoked in some of the items. Future research should therefore examine whether communitas, as operationalised here, captures relational experiences in cultural contexts where the boundaries between self and group are conceived differently. In many non-WEIRD settings emphasizing interdependence rather than individualism (Markus & Kitayama, 2010), collective participatory events already presuppose forms of interconnectedness that might render experiences of communitas or ego-dissolution less phenomenologically distinct, or attenuate the psychological benefits observed in the current WEIRD sample. To enhance cross-cultural generalisability, future adaptations of the scale should thus involve participatory translation and validation within cultural contexts where

collective psychedelic experiences are integrated into normative practices, such as the Brazilian Ayahuasca religions (Labate & Feeney, 2012; Labate & MacRae, 2016). Such work could help determine whether psychedelic communitas represents an articulation of a more fundamental human capacity for collective transcendence during psychedelic states, or whether its current operationalisation primarily reflects WEIRD phenomenological and linguistic assumptions.

The sample characteristics also call into question to what extent biases toward the positive effects of psychedelics may have led to demand characteristics influencing study outcomes–which should be considered by addressing participant expectations and biases in future studies. Furthermore, heterogeneous approaches to the preparation, administration, and communication of drug doses in ceremony settings made it impossible to control for the quantity or potency of substance consumed by participants. Lastly, retreat settings in remote locations may have been visited by participants as part of more extensive journeys, meaning that the assessed psychological variables may have been confounded by additional travel experiences, which are known to positively affect mental and physical health (Chen & Petrick, 2013).

With an increasing number of completed clinical trials and growing datasets of naturalistic psychedelic use, a salient question for future research lies in the comparison of the two. Acknowledging the obvious safety benefits of highly controlled clinical and laboratory environments, the current findings suggest that certain elements in naturalistic settings, particularly their collective dimension, may hold a unique potential for enhancing positive outcomes of psychedelic use. Detailed assessment of clinically relevant variables will allow future studies to expand on the current results by exploring the therapeutic potential of collective experiences in populations suffering from specific mental illnesses. Specifically in

the case of posttraumatic stress for example, authors have discussed the value of therapeutic rituals (Johnson et al., 1995), self-disclosure (Bowen et al., 2010), and strong communities (Bracken, 2002). While observational studies on psychedelic effects cannot replace randomized controlled trials, their findings may inform new treatment avenues by uncovering psychological mechanisms that could not be explored in smaller samples or including patient populations that have not yet been treated with psychedelics in clinical settings (see e.g., Spriggs et al., 2021).

The abovementioned prerequisites of economic and physical mobility for accessing the psychedelic group experiences studied here highlight another significant limitation common to group-based mental health interventions more generally: Some of the populations most affected by social isolation and loneliness—such as older adults (Tomida et al., 2024), individuals with physical disabilities (Emerson et al., 2021), or those with serious illnesses (Rokach, 2003)—often also face impaired physical mobility. This impairment hampers their ability for social participation and complicates access to potentially therapeutic psychosocial interventions (Islam & Jaffee, 2024; Rosso et al., 2013; Tomida et al., 2024), including also psychedelic interventions (Gray et al., 2023). The next chapter will present a novel intervention that aims to overcome several of these limitations by reproducing prolonged group-based self-transcendent experiences in a VR environment, with the intention to improve psychoemotional symptom burden in people suffering from life-threatening illnesses.

Chapter 5: A *Numadelic* VR Group Experience for People with Life-threatening Illnesses

5.1 Background

Modern medicine has produced a wide range of approaches to treating the physical body of patients with life-threatening illnesses (LTIs), up to the moment of death. However, fewer resources are available to support patients in managing the fear, uncertainty, and loneliness that often accompany LTI diagnoses (Ho et al., 2023; Pitman et al., 2018). LTIs can exact a substantial psychosocial burden due to fear of death, reduced physical mobility and fatigue induced by illness or medications, increased time spent on procuring medical services, and associated social isolation (Rokach, 2003). Although up to 40% of cancer patients meet the criteria for mood disorders (Mitchell et al., 2011), evidence-based treatments for supporting mental health and well-being in patients with LTIs are limited and often difficult to access. Current treatments primarily include talk therapy and medications such as serotonin-selective reuptake inhibitors (SSRIs) or benzodiazepines (Grassi & Riba, 2014), which are, however, limited in their effectiveness for people with LTIs. For example, pharmacological depression treatments have been found to be less effective in the LTI population compared to adults suffering from non-LTI related depression (Ostuzzi et al., 2018). The development of novel and innovative treatment modalities to support the mental health of people with LTIs is thus urgently needed, and there has been recent increased interest in developing new technologies, including VR experiences, to support this population (Carmont & McIlfatrick, 2022; Martin et al., 2022; Mo et al., 2022; Woo et al., 2024).

In recent years, there has been renewed interest in the use of psychedelic drugs, such as psilocybin, for people facing LTI (Anderson et al., 2020; Gasser et al., 2015; Griffiths et al.,

2016; Grob et al., 2011; Holze et al., 2023; Ross et al., 2016; Yu et al., 2021), including group-based psychedelic therapy (Lewis, Byrne, et al., 2023; Lewis, Garland, et al., 2023). Results indicate that these individuals can experience rapid and sustained reduction in symptoms of anxiety and depression following psychedelic-assisted therapy (PAT) (Ross et al., 2016). While the mechanisms of action driving the benefits of PAT are a matter of continued research, there appears to be a strong relationship between the occurrence of psychedelic-induced self-transcendent experiences (STEs) and the mental health benefits reported by people with LTIs (Griffiths et al., 2016). This is consistent with research suggesting that the efficacy of psychedelics in therapeutic settings depends on the acute subjective experience during the session (Roseman et al., 2019; Roseman et al., 2018). One study has found similarities between the experience elicited by the psychedelic N,N-Dimethyltryptamine (DMT) and near-death experience (NDE) reports (Timmermann et al., 2018), which could be another explanation for the efficacy of psychedelics in LTI populations, considering that NDEs can lead to drastic reductions in fear of death (Pehlivanova et al., 2023). Unfortunately, PAT is challenging to implement on a broad scale in the LTI population, owing to legal restrictions, high cost of delivery, and side effects (Muttoni et al., 2019). Even as psychedelics become more widely available and socially acceptable, limitations to access will remain for many people with LTIs, including frailty or use of medications that render psychedelics contraindicated. Finally, many individuals may not feel comfortable taking psychedelics, considering their intense subjective effects and stigma surrounding their use. Thus, solutions that deliver some of the benefits of PAT in people with LTIs, without its limitations, would be highly desirable.

Group-based VR interventions have been shown to offer unique potential in addressing issues of loneliness and isolation in patient populations with limited mobility or ability to participate in social life, including patients in residential care (Brimelow et al., 2022; Gaspar

et al., 2018), aphasic stroke patients (Marshall et al., 2020), and individuals suffering from social anxiety (Anderson et al., 2017; Anderson et al., 2013; Ngai et al., 2015) or social phobia (Salehi et al., 2020). The need for novel interventions that include social support for people facing LTIs is further exacerbated by the fact that loneliness and social isolation do not only increase symptom burden (Abedini et al., 2020) and reduce quality of life (Dahill et al., 2020; Hyland et al., 2019), but are also associated with increased mortality following a diagnosis (Drageset et al., 2013). Although extended, interactive, group-based VR interventions therefore hold a unique potential for patients with restricted mobility, studies on the use of VR for the LTI population have thus far mostly employed solo experiences involving photorealistic or 3D content viewed in a single session (Carmont & McIlfatrick, 2022; Martin et al., 2022).

Recently, Glowacki et al. (2020, 2022) described the design of multi-user VR experiences using a so-called 'numadelic aesthetic', (from Greek *pneuma*: 'breath', 'spirit' or 'soul', and *delein*: 'to reveal' or 'to manifest'), a weakly representational visual approach inspired by near-death phenomenology (Glowacki, 2024). Whereas most VR applications aim for photorealistic fidelity, numadelic representations are intentionally abstract, dissolving conventional spatiotemporal distinctions between self and other to achieve a sense of connectedness and unity. Compared to typical metaverse avatars, which represent bodies as highly detailed, the numadelic aesthetic represents participants as luminous energetic essences with diffuse boundaries, as illustrated in Figures 5.2 and 5.3 below. "Isness," a guided multi-person VR experience designed within this numadelic aesthetic, was found to elicit self-transcendent experiences (STEs) comparable to those following a moderate dose of psilocybin (Glowacki et al., 2020), using a range of psychometric measures, including the Mystical Experiences Questionnaire (MEQ-30) (Griffiths et al., 2006; MacLean et al., 2012), Inclusion

of Other in Self (IOS) Scale, Ego Dissolution Inventory (EDI) (Nour et al., 2016), and the Communitas Scale described in the previous chapter (Kettner et al., 2021).

Building on this work, the present study intended to test the feasibility and potential benefits of a multi-session, group-based intervention of numadelic VR experiences, video calls, and group text chats, called 'Clear Light' (CL), for reducing the psychosocial symptom burden in people with LTIs. Using an open-label, observational cohort design, effects of the CL program were prospectively assessed on a range of clinically relevant self-report measures, including depression, anxiety, and psychological well-being in LTI patients. It was hypothesized that participation in the CL program would lead to statistically significant reductions in symptoms of anxiety and depression, while improving mental well-being. Additionally, measures of demoralization, connectedness, spiritual well-being, and death acceptance were included as exploratory secondary outcomes.

5.2 Methods

5.2.1 Participants

Ethical approval for this study was granted by the Imperial College Joint Research Compliance Office (JRCO) and the Imperial College Research Ethics Committee. CL program organizers sent out a link to the study website to program participants. CL itself was advertised by word of mouth and via a website (https://anuma.com/clearlight). Criteria for participating in the CL program included 1) self-reporting a LTI diagnosis; 2) speaking fluent English; 3) residing in the United States, Canada, or United Kingdom; 4) being physically able to engage with the VR activities (e.g., being able to sit upright for approximately one hour and tolerating

VR sufficiently well with no significant VR sickness); and, 5) being cognitively able to engage with the program activities (e.g., not suffering dementia).

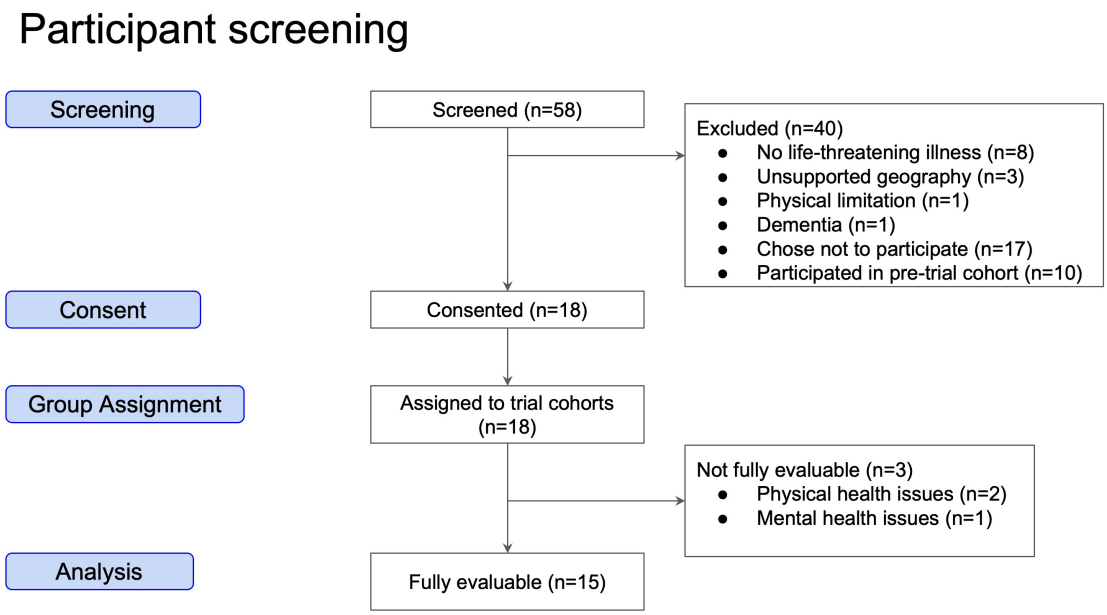


Figure 5.1 CONSORT-style Participant Flow Diagram. This figure has been reproduced with permission from Kettner et al., (2024). CONSORT: Consolidated Standards of Reporting Trials

A total of 58 individuals filled out a web form indicating interest in participating in CL (Figure 5.1). Of those individuals, 23 were excluded due to not fulfilling one of the above criteria, 17 chose not to participate and 10 participated in pre-trial cohorts whose feedback was used to improve the CL experience. Of the 17 participants who were categorized as "Chose not to participate," 6 indicated that none of the available times offered for sessions would work within their schedules. Seven participants stopped responding to communications (i.e. lost contact) prior to the consenting process. Four participants indicated they did not wish to participate for other personal reasons.

A total of 18 participants screened into the CL program gave consent to participate in the present observational study. Two participants were excluded from the analysis because they

had dropped out prior to completing the program following hospitalization due to their illnesses. A third participant was excluded from the analysis because they reported a mental health emergency related to a psychedelic experience unrelated to the CL program or the present study, resulting in a total of 15 fully evaluable participants. Participants were initially divided into 3 cohorts of 6 participants, run sequentially between July and October 2023. There were 6, 5, and 4 fully evaluable participants in the first, second, and third cohorts, respectively.

5.2.2 Design of the Clear Light Program

All cohorts were facilitated by the same facilitators, one male and one female. The CL program is composed of four distributed VR sessions, bookended by two video conference calls (Zoom Video Communications, Inc.) with asynchronous, encrypted group text chats (WhatsApp, Meta Platforms, Inc.) interspersed throughout. The CL environment was developed using the aNUmaXR experience creation platform (aNUma, Inc.) and delivered on Meta Quest 2 VR devices (Meta Platforms, Inc.). The creators and facilitators of the CL experience, including authors D.R.G., J.W., and J.L.H., were employed or contracted by aNUma, Inc. at the time of the study, and are shareholders, as is R.C.-H. (see Conflict of Interest section at the end of the manuscript).

The content of each of the six sessions is presented below and in Figure 5.2.

1. ***Orientation*** (video conference, ~90 minutes). The first session allowed participants to get to know each other and to meet the facilitators. Participants shared information about themselves, including how they were relating to their LTI, as well as their attitudes towards mortality. The facilitators explained the logistics and purpose of the program, and participants had an opportunity to ask any questions they had at that time.

2. ***Preparation*** (VR, 20-40 minutes). This session was a one-on-one session between each participant and a facilitator or other study staff in which participants were introduced to the VR hardware, including connecting the VR Head Mounted Display to WiFi, setting up a VR boundary, and starting the VR app (aNUmaXR). Once the participant launched the aNUmaXR app, they were met in the virtual environment by the facilitator or study staff. Participants then completed a short experience that included a guided meditation technique later used in the group sessions.
3. ***Life*** (VR, ~60 min). The focus of the first group VR session was the life review, an evidence-based practice described first by Butler (1963), augmented by a VR visualization. Visualizations included a sequence in which the participants observed an abstracted version of themselves ("energetic reflection") grow through life stages from infancy into adulthood, supported by an audio narrative.
4. ***Boundless*** (VR, ~60 min). The fourth session was centred on an out-of-body experience in which participants' points of view were moved from first person to a third person perspective, meaning they could observe themselves and their movements in real-time from further back and above. This was accompanied by a narrative that explored the relationship between consciousness and the corporeal body. Participants were told they would go on a short journey where they will extend our field of awareness beyond the boundary of their bodies. As their perspective shifts out of their avatars, they are asked how it feels to observe their body from afar and to imagine their conscious awareness merging into a broader field of awareness.
5. ***Offering*** (VR, ~60 min). In the final group VR session, participants went through a series of sharing rounds that was more extended than in previous sessions. First, each participant described something that they would like to let go of and simultaneously "deposited" energy from their body into a central element. Later, each participant re-

entered the central element and "received" energy back into their avatar while sharing something that they felt they needed more of in their lives at that moment.

6. ***Integration*** (video conference, ~90 min). The final session was a facilitated group conversation where participants could reflect on the experiences that they had together throughout the program. It was also an opportunity to discuss how to take what was learned and gained through the program into everyday life going forward.

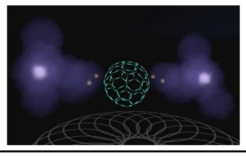
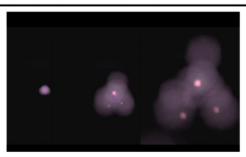
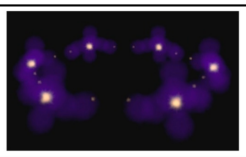
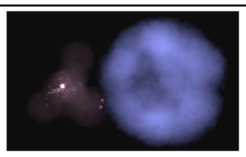
Session	Themes & aims	Exercise	Visual reference	
1. Introduction	Orientation; building group cohesion			
2. Preparation VR	Comfort handling the VR device; familiarization with virtual self-representation	Introduction to virtual 'energy body'		*Participants use hand gestures to move their virtual 'energy bodies' and interact with a central object*
3. Life VR	Life stages; narrative self and identity	Life review		*While sharing their life review, participants view their 'energetic reflections' grow, representing stages of their lives*
4. Boundless VR	Continuity of consciousness; corporeal self; impermanence	Out-of-body experience		*Participants' cameras pan out so that they view themselves from an out-and-above perspective in real-time*
5. Offering VR	Letting go and openness; blurring of boundaries	Letting go and receiving		*A participant moves into a large glowing orb to symbolically deposit what no longer serves them and receive what they seek*
6. Integration	Collective meaning-making; take-aways from the program			

Figure 5.2 Structure of the Clear Light Program. This figure has been reproduced with permission from Kettner et al. (2025).

In each VR session, participants appeared as diffuse and dynamic clouds of colour (see Figures 5.2, 5.3), intending to substitute the physicality of embodiment with the impression of the body as energy. Participants' hands were similarly figured as concentrated energetic luminosity, and simple environmental objects populated the space at various times. Each VR

session also included a curated soundtrack of ambient recorded music that was designed to match with the ongoing visual experience.

Each session also included guided meditations by facilitators and elements of embodiment practice. Most sessions also included rounds of sharing in which participants respond to prompts (e.g., 'What does "letting go" mean to you?'; 'How would you describe your process of releasing attachments or surrendering control?'). During sharing rounds, participants discussed how they were feeling regarding their LTI and were encouraged to engage in active listening with one another.

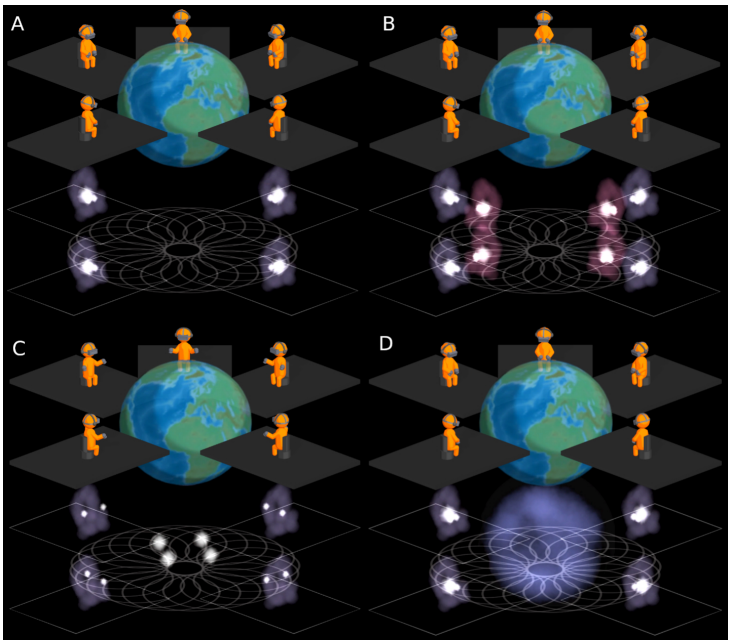


Figure 5.3 Schematic Representation of the Group 'Numadelic' VR Setup. The top section of each panel represents individuals in physical space, seated with VR headsets and holding controllers. The lower section shows participants' energy body avatars as purple clouds in the virtual environment. The large white light in the centre of each avatar is located at and represents the avatar's heart, while the two smaller lights follow the participant's hand movements. Panel A represents the general setup, in this case showing four participants and one facilitator, with their hands in resting position. Panel B shows a schematic from Session #2 "Life" in which participants interact with their "energetic reflections" represented as maroon energy bodies. Panel C represents an exercise from Session #3 "Boundless" in which participants can share their heart lights into the centre of the circle by spreading their arms. Panel D illustrates an exercise from Session #4 "Offering", during which participants enter one-by-one into a large blue light sphere in the centre of the circle in two distinct rounds. In the first round, they discuss something they would like to let go of and simultaneously "leave behind" the light energy from their body. Later, each participant re-enters the light and "receives" energy back into their avatar while sharing something they feel they need more of in their lives now. This figure has been reproduced with permission from Kettner et al., (2025).

In addition to video calls and VR sessions, participants were able to communicate with other members of the cohort and facilitators asynchronously via WhatsApp. Facilitators provided prompts to generate contemplation and discussion within the group, which were designed to prepare participants for the upcoming sessions.

5.2.3 Measures

Participants were assessed within one week prior to the start of the program and again one week after it ended, a total of 5 weeks apart. Participants completed surveys on their personal computers or smartphones through a secure, encrypted interface (Alchemer, LLC).

The following primary outcomes were included:

- Hospital Anxiety and Depression Scale (HADS), assessing symptoms of anxiety and depression (Snaith, 2003). There are 7 questions each related to anxiety and depression. Possible responses vary per question and are coded from 0-3, for a minimum possible score of 0 (least anxious or depressed) and a maximum possible score of 21 (most anxious or depressed) for each subscale. Improvements correspond to lower scores.
- Short Warwick-Edinburgh Mental Well-being Scale (sWEMWBS), a 7-item measure of psychological well-being (Tennant et al., 2007). Each item is a 5-point Likert scale ranging from “None of the time” (coded as 1) to “All of the time” (coded as 5). The minimum score is 7 (lowest mental well-being) and maximum score is 35 (highest mental well-being). Improvements correspond to higher scores.

Several measures were included as exploratory secondary outcomes:

- Demoralization Scale (DS-II) assessing hopelessness, helplessness and their impact on an individual's overall well-being in the context of a serious illness (Kissane et al., 2004). Due to an oversight setting up the survey, 1 of the 16 items on the scale was

never presented to participants. Participants rated each of the 15 items related to their feelings of demoralization on a 3-point Likert scale with "Never" coded as 0, "Sometimes" coded as 1, and "Often" coded as 2. The minimum score is 0 (least demoralized) and the maximum score is 30 (most demoralized). Improvements correspond to lower scores.

- Watts Connectedness Scale (WCS). This scale was developed in the context of psychedelic research and measures an individual's sense of connectedness to self, others, and the world (Watts et al., 2022). Participants rated the 19 items on a visual reference scale that ranged from 0 = "Not at all" to 100 = "Entirely." Presented scores represent the average item score after reverse coding where required. The minimum score is 0, indicating least connected and the maximum score is 100, indicating most connected. Improvements correspond to higher scores.
- Functional Assessment of Chronic Illness Therapy - Spiritual Well-Being (FACIT-Sp), assessing spiritual well-being in the context of chronic illness (Peterman et al., 2002). Due to a technical issue with the survey tool, only the first 10 items (of 12 total) were reliably delivered to participants. The sum of those 10 items were analysed. Participants rated items related to their spiritual well-being on a 5-point Likert Scale from "Not at all" to "Very much," with 3 items reverse coded. Items are coded from 0 (lowest spiritual well-being) to 4 (highest spiritual well-being). The totals range from a minimum of 0 to a maximum of 40. Improvements correspond to higher scores.
- Death Attitude Profile-Revised (DAP-R), of which the Fear of Death and Death Avoidance subscales were used (Wong et al., 1994). Participants rated the 12 items related to their negative death attitudes on a 7-point Likert scale ranging from "Strongly disagree" (coded as 1) to "Strongly agree" (coded as 7). The minimum score is 12 (least

negative), and the maximum is 84 (most negative). Improvements correspond to lower scores.

As part of the post-program survey, participants were asked to rate on a scale of 0-10 whether they would recommend the experience to other individuals facing a LTI, referred to as Net Promoter Score (Reichheld, 2003).

5.2.4 Statistical Analysis

A Repeated Measures Multivariate Analysis of Variance (RM MANOVA) was performed to test pre- to post-intervention changes across the 7 dependent variables. Multivariate significance is reported via the Wald-type statistic (WTS) (Randall et al., 1997) and modified ANOVA test statistic (MATS) (Friedrich & Pauly, 2018) which is robust against deviations from symmetry and heteroscedasticity. Levene's test statistic was calculated for each outcome measure. To then examine univariate changes at the level of individual outcome measures, a two-tailed within-subjects t-tests was conducted as follow-up. For each outcome variable, Hedges' g effect size was calculated and interpreted along the empirical guideline for social psychology of 0.15, 0.40 and 0.70 for small, medium, and large effects respectively (Lovakov & Agadullina, 2021). While uncorrected p-values are reported for follow-up tests, any secondary outcome measures that would not survive Bonferroni correction are pointed out.

5.3 Results

5.3.1 Participants

The mean age of the 15 fully evaluable participants was 66.7 (SD = 8.8). All indicated their ethnicity as White. Thirteen participants were female and 2 were male. Thirteen of the

participants were from the United States, 1 was from the United Kingdom, and 1 was from Canada. All 15 participants self-reported life-threatening illnesses, including advanced cases of cancer (n = 12), heart disease (n = 2), and lung disease (n = 1).

5.3.2 Changes in Primary Outcomes

Levene's test showed no deviations from homoscedasticity in any of the 7 analysed outcome measures. RM MANOVA revealed significant multivariate differences between pre- and post-intervention scores ($F(1, 28) = 13.16$, $p < .001$, WTS = 30.5, MATS = 13.2).

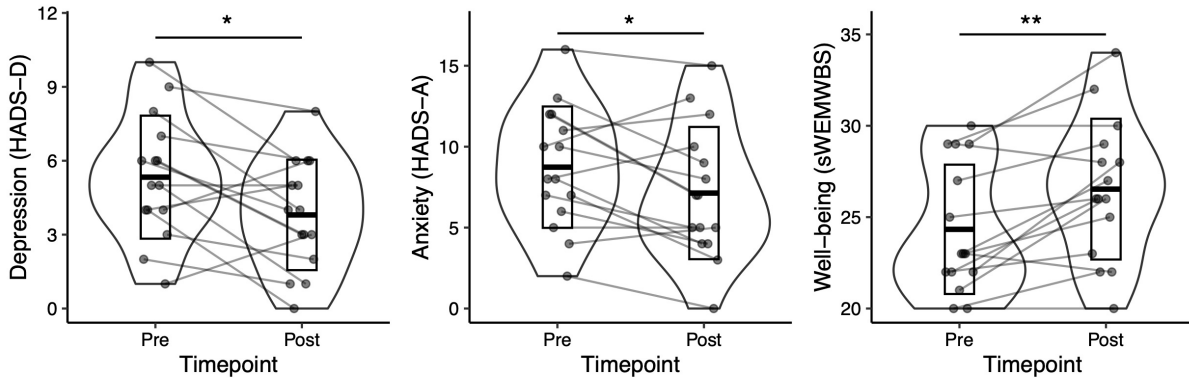


Figure 5.4 Changes in Primary Outcomes. Mean scores measured one week before (Pre) and after (Post) participation in the Clear Light VR program are shown including standard error (SE) and individual participant data (N=15).

* indicates $p < .05$, **$p < .01$

Follow-up t-tests showed that all three primary outcome measures were significantly improved at the post-intervention time point (Figure 5.4, Table 5.1). At baseline, considerable levels of anxiety and depression symptoms were reported by 60% (9/15) and 20% (3/15) of participants, respectively, based on the HADS (cutoff score > 7, see Table 5.1). The mean pre-program HADS-A score was 8.73 (SD = 0.97) and the post-program mean was 7.13 (SD = 1.05), which was significantly lower ($t(14) = 2.4$, $p = .030$) with a moderate effect size (g = 0.40). The pre-program mean depression score (HADS-D) was 5.33 (SD = 0.64), which

fell to 3.80 (SD = 0.58) post-program. This difference was significant ($t(14) = 2.8$, $p = .015$) at a medium-large effect size (g = 0.63). Well-being (sWEMWBS) scores increased from 24.33 (SD = 0.91) to 26.53 (SD = 0.99) post-program, which was also significant at a moderate effect size ($t(14) = -3.8$, $p = .002$, g = 0.58).

5.3.3 Changes in Secondary Outcomes

Among the secondary outcomes, significant improvements were detected among all measures except for death attitudes (DAP-R, $t(14) = -1$, $p = .31$). The greatest improvements were observed for connectedness (WCS), which significantly increased from 66.63 (SD = 4.65) to 76.25 (SD = 4.02) post-program ($t(14) = -4.0$, $p = .001$, g = 0.55). Demoralization (DS-II) was found to be reduced from 9.47 (SD = 1.29) to 7.00 (SD = 1.48), ($t(14) = 2.5$, $p = .028$, g = 0.45), although this effect would not have been significant at 7-fold Bonferroni-correction. Spiritual well-being (FACIT-Sp) was increased from 26.20 (SD = 1.99) to 29.93 (SD = 1.88, $t(14) = -4.0$, $p = .001$, g = 0.48).

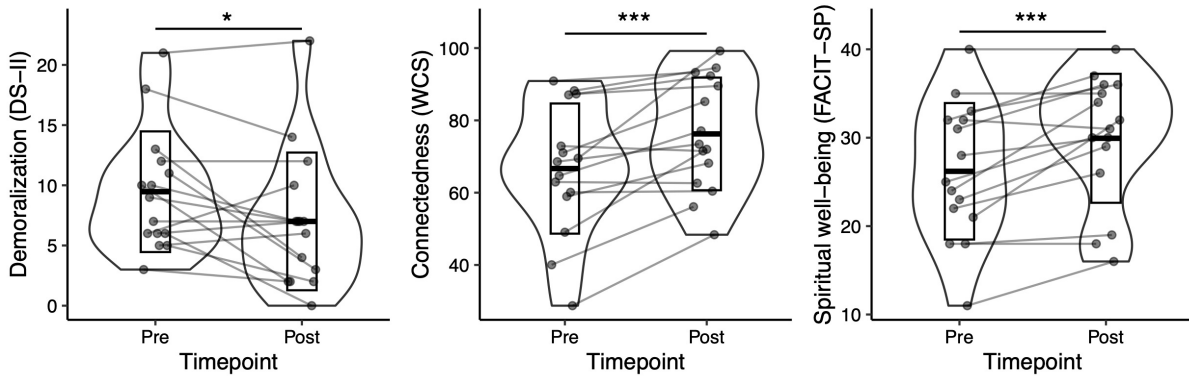


Figure 5.5 Changes in Secondary Outcomes. Mean scores measured one week before (Pre) and after (Post) participation in the Clear Light VR program are shown including standard error (SE) and individual participant data (N=15).

* indicates p < .05, ***p < .001

The mean score on the Net Promoter question was 8.93 (SD = 0.27) out of a possible 10. The Net Promoter Score (NPS) was 60 (Reichheld, 2003), with 6 participants indicating a score of 10, and the lowest score being 7.

Table 5.1 Results across all Prospective Outcome Measures

Outcome	Pre (SE)	Post (SE)	*p*	Hedges' g
HADS-A	8.73 (0.97)	7.13 (1.05)	**.030**	0.40
HADS-D	5.33 (0.64)	3.8 (0.58)	**.015**	0.63
sWEMWBS	24.33 (0.91)	26.53 (0.99)	**.002**	0.58
DS-II	9.47 (1.29)	7 (1.48)	**.028**	0.45
WCS	66.63 (4.65)	76.25 (4.02)	**.001**	0.55
FACIT-Sp	26.2 (1.99)	29.93 (1.88)	**.001**	0.48
DAP-R	31.33 (3.49)	29 (2.86)	.313	0.18

Note. Mean scores (N=15) measured one week before (Pre) and after (Post) participation in the Clear Light VR program are shown including standard error (SE). DAP-R: Death Attitude Profile-Revised; DS-II: Demoralization Scale II; FACIT-Sp: Functional assessment of chronic illness therapy – spiritual well-being; HADS-A/-D: Hospital Anxiety and Depression Scale, Anxiety and Depression Subscales; sWEMWBS: short Warwick-Edinburgh Mental Well-being Scale; WCS: Watts Connectedness Scale.

5.4 Discussion

This observational cohort study followed individuals facing a LTI from before to after their participation in a group-based multimedia (VR, video and text chat) program. It demonstrated the feasibility and potential benefits of the program, showing significant improvements in psychological and spiritual well-being, connectedness, anxiety, depression, and demoralization. It is possible to conclude that the intervention is operationally feasible in that it was successfully deployed to 15 participants in three different countries, with each participant connecting to the VR and Zoom sessions from their own homes using equipment received via mail. Participants found the intervention tolerable (i.e. were able to complete the sessions without significant complaints about VR sickness), and participants indicated (average

rating of 8.93 out of 10) that they would recommend the program to others with a similar condition. The present findings thereby add to the limited body of literature demonstrating the feasibility and beneficial effects of VR interventions on well-being (McGhee et al., 2024) and other secondary symptoms (Ioannou et al., 2020) in palliative care patients, while to our knowledge representing the first ever use of a group-based VR experience in LTI patients.

Although there was significant variability across the assessed outcomes, the observed improvements were moderate for all significant measures, being highest for depression, well-being, and connectedness, followed by spiritual well-being, demoralization, and anxiety. With an average effect size of $g = 0.52$, the results were comparable to other psychosocial interventions for death anxiety (Menzies et al., 2018), following a similar pattern as found following psychotherapy in palliative care, insofar as depression and quality of life showed greater improvements than anxiety (Fulton et al., 2018). The magnitude of improvements was similar to those found for psilocybin treatment for end of life, although the three published clinical trials showed a great amount of variability in their effect sizes (Yu et al., 2021). Notably, significant effects could be detected in the present sample despite baseline depression and anxiety scores being on average within or close to the healthy normal (< 8) range. Further research should thus examine the effects of the here-studied intervention in a selectively recruited sample consisting of more severely depressed or anxious patients.

This study did not find statistically significant changes on the DAP-R (Fear of Death and Death Avoidance subscales). It is not possible to draw strong conclusions about this null result from the small sample observed in this study, and future research is warranted to determine why the hypothesized improvement was not found. If the failure to find such an effect is due to random variability in the sample or relatively low sensitivity of the DAP-R,

then a statistically significant improvement may be observed in a larger sample. It is also possible that participants did not experience reduced fear of death or improvement in their death attitude. Such a conclusion would raise the intriguing possibility that the benefits of the program are mediated through a different (possibly more general) psychological mechanism than changing attitudes toward death. Future research that utilizes larger sample sizes and additional measures of death attitudes could tease apart these possibilities.

While the present study was not aiming to explore the mechanisms underlying the intervention presented here, it is likely that a combination of intra- and inter-personal processes generated the observed mental health improvements. The numadelic representational aesthetic was designed to model aspects of self-transcendent and near-death experiences (STEs and NDEs, respectively), including an out-of-body sequence modelled on that described by Glowacki (2024), and a sequence where each participant merged with a luminosity substantially larger than themselves. NDEs are sometimes able to dramatically diminish anxiety associated with death (Bianco et al., 2019; Tassell-Matamua & Lindsay, 2016), with the extent of death anxiety reduction seemingly correlated with NDE intensity (Greyson, 2015). Prior studies have shown that VR can effectively be used to generate NDE-like states (Barberia et al., 2018) and out of body experiences (Martial et al., 2023) which were able to attenuate fear of death in healthy participants (Bourdin et al., 2017). The CL program assessed in this study augmented similar STE and NDE-evoking elements with narrative support techniques shown to be effective in supporting the mental health and well-being of patients with LTIs (Rosenfeld et al., 2018).

The fact that the above-described experiences took place in a group, rather than alone, with ample opportunity to discuss and reflect in sharing rounds mediated by trained facilitators,

was hoped to further establish psychosocial resources known to affect the quality of life in people suffering from LTIs. Several meta-analyses have shown the positive mental health effects of peer support groups for people with LTIs (Meyer & Mark, 1999; Rehse & Pukrop, 2003), including online-based support groups (Ihrig et al., 2020; Rains & Young, 2009), although recent studies have shown that face-to-face peer support is perceived as more beneficial (Huber et al., 2018) and more desirable (Boyes et al., 2018) than seeking support online. Importantly, the VR modality used in the present intervention has previously been shown to elicit experiences of togetherness and shared humanity among participants comparable to real-life group sessions (Glowacki et al., 2022). Together, these findings suggest that the presented VR intervention may have the potential to leverage some of the advantages of embodied peer contact while remaining accessible to subjects with limited mobility, who would not otherwise be able to easily partake in face-to-face peer support.

Previous approaches using VR to support people with LTI differ from the strategies used in the CL program described here in several ways. Major differences include: 1) Previous studies typically involve one VR session, whereas CL is comprised of a series of modules that take place over several weeks. 2) Where previous studies have relied on solo VR experiences (Mo et al., 2022), the group aspect of CL allows participants to support and share with one another. 3) Most previous approaches have implemented 360-video as a passive viewing experience. Participants in the CL program can interact within the virtual world through speech and movements, meant to create a sense of embodied agency. 4) Most VR approaches rely on near-photorealistic content (e.g., 3D images and videos of nature scenes in Ferguson et al., 2020; Johnson et al., 2020; Niki et al., 2019) and photo-realistic avatars (M. Dang et al., 2021), which can create an "uncanny valley" effect (Seyama & Nagayama, 2007). CL's numadelic aesthetic uses a weakly representational approach, in which avatars appear as energy bodies

with soft boundaries in a visually sparse environment that do not resemble anything encountered in the 'real world'. As such, CL attempts to stimulate endogenous meaning-making, inviting participants to project their own meaning into the visual content, comparable to how meaning is projected onto a Rorschach plot. 5) Finally, most VR studies have focused on a single technique, such as relaxation (Baños et al., 2013; Woo et al., 2024) or life review (P. Dang et al., 2021), in contrast to the multimodal approach implemented within CL.

Study limitations and future directions. The observational design employed in the current study imposes several inherent limitations, including the lack of randomization, control condition, or the targeted recruitment of a more ethnically or gender diverse, or more clinically defined study sample. In particular, this study lacked gender (mostly female) or ethnic (entirely White) diversity. Self-selection bias might have led to the inclusion of participants who had a particularly high potential to benefit from this intervention. Future study designs should incorporate a thorough inventory of any medications or other substances that participants are currently taking or plan to take. For example, knowing the chemotherapy regimen of cancer patients would be helpful for covariate analyses. These studies should also exclude individuals who intend to use mind-altering substances, such as psychedelics, during the study period.

Additionally, the design does not allow us to draw strong conclusions about the mechanisms of action of the intervention. The extent to which the VR sessions, or interactions with facilitators, or other participants during group calls may have contributed to improved mental health outcomes remains unclear based on the present results. In future studies, the specific impact of the different stages of the CL protocol could be elucidated through the inclusion of additional intermittent assessments and/or measures assessing potentially mechanistic variables pertaining to VR and group therapeutic experiences. For example, prior

studies investigating a single-session, group, numadelic VR experience have demonstrated subjectively reported effects of ego dissolution, communitas, and mystical-type experiences akin to psychedelic drug effects (Glowacki et al, 2020, 2022). Assessment of relational constructs, such as therapeutic rapport and group cohesiveness throughout the program could shed light on the respective contribution of intra- and intersubjective mechanisms to the here observed therapeutic outcomes. Although challenging to integrate with a remote participation design, advances in combined VR-neuroimaging applications (Li et al., 2024) may enable future studies to further delineate similarities and differences in VR- and psychedelic-induced brain states and to explore the potential of interpersonal neural synchrony if used in a hyperscanning design. Lastly, analyses of follow-up assessments will be required to draw any conclusions about sustained responses beyond the here-reported endpoints at one-week post-intervention.

The creators and facilitators of CL were affiliated with the for-profit, public benefit corporation that provides CL. Therefore, they had a financial interest in the success of the program, constituting a potential source of bias. Unintentional bias could have been introduced in a variety of ways, for example, in study design and in the interaction with participants. Further research by outside groups without such financial interest is warranted. It is important to note that the success of such a program may depend on the intention and effort of the facilitators and other staff to provide a good experience, so quality control will be an important component of any future research.

The existential and psychological implications of mortality are rarely discussed in secular modern societies (Hvidt & Assing Hvidt, 2019), although research indicates that structured engagement with one's own mortality can improve quality of life and psychological

well-being at the end of life (LeMay & Wilson, 2008). People with LTIs often encounter additional challenges when trying to access peer support, or any of the limited set of treatments available to support their mental health and well-being. We presented an observational cohort study of a novel group-based VR intervention, demonstrating its feasibility and potential benefits in improving symptoms of depression and anxiety in patients with a LTI diagnosis, while enhancing psychological and spiritual well-being and connectedness. These preliminary findings warrant further randomized, controlled studies, especially considering the scarcity of existing treatment options that can provide psychosocially supportive experiences to individuals who suffer from mobility-impairing serious illnesses.

Chapter 6: General Discussion

This thesis set out to investigate the psychosocial mechanisms underlying psychedelic experiences across clinical and naturalistic contexts. Across three empirical studies, the findings converge to support the central claim that psychedelics operate not merely through pharmacological means, but through complex, dynamic interactions between drug, person, and their social environment. These interactions, examined through the lenses of therapeutic alliance in an RCT of psilocybin for major depression (Chapter 3), group-based communitas at psychedelic retreats (Chapter 4), and a multi-user virtual reality program inspired by psychedelic phenomenology (Chapter 5), highlight the value of an enactive biopsychosocial model of psychedelic action. Rather than treating psychosocial factors as confounds or secondary to the pharmacological effect of the intervention, the present findings argue for their centrality: relational dynamics do not only shape the unfolding of psychedelic experiences but also mediate their long-term effects on mental health and well-being. Taken together, the findings underscore the importance of relational and contextual factors in shaping therapeutic outcomes, offering empirical support for the notion that acute and long-term psychedelic effects may unfold through circular causal processes across biological, psychological, and social domains.

To further elaborate on this integrative perspective, the following sections will revisit each empirical chapter, reflecting on key findings and contributions to a biopsychosocially embedded understanding of psychedelic effects.

6.1 Integrating Results Through an Enactive Biopsychosocial Lens

6.1.1 Therapeutic Alliance in Psilocybin Therapy

Chapter 3 explored how the dyadic relationship between patient and therapist impacts the psychedelic experience and long-term outcomes in patients diagnosed with MDD. As hypothesised, therapeutic alliance assessed before dosing sessions had a significant effect on depression outcomes, mediated by an intensification of subjective drug effects, including mystical-type and emotional breakthrough experiences. The design of the study, including two successive dosing sessions, revealed that rather than operating in a linear cause-effect sequence, alliance became part of a mutually- and self-reinforcing positive feedback process—a felt sense of safety and trust that allowed patients to let go more deeply into the psychedelic state, in turn improving not only depressive symptoms, but also the relational attunement between sessions. From an enactive perspective, this reflects the circularity between interpersonal context and intrapsychic process: the quality of the therapeutic relationship influences the emergence of psychedelic states, as much as it is itself shaped by the emotional and cognitive shifts induced by the drug's neurobiological effects.

In psychotherapy more broadly, therapeutic alliance has similarly been found to enter into reciprocal positive feedback loops with symptom improvements, especially early in treatment (Flückiger et al., 2020). The comparison of psychedelic-assisted therapy (PAT) to early-stage psychotherapy seems particularly fitting insofar as the hybrid pharmaco-psychosocial nature of PAT may involve a greater quantity of client-therapist interaction than conventional pharmacotherapy, but still much less so than what would be delivered over a course of regular psychotherapy. It is therefore likely that the experience of alliance present in most settings of PAT, including the one in Chapter 3, is primarily a function of trait-like components of alliance, i.e. patients' general tendency to form strong relationships (Zilcha-

Mano, 2017; Zilcha-Mano & Fisher, 2022). On the other hand, the strength of the observed reciprocal effect of emotionally cathartic experiences on alliance before the following session suggests that the psychedelic experience may also function as a catalyst for the therapeutic relationship. This could correspond to an accelerated introduction of state-like aspects of alliance into the treatment process, although the relatively short duration of the treatment limits the potential for session-specific dynamics in the relationship between therapist and client. Experiences of rupture, repair, and negotiation, which contribute to the complexity of the therapeutic relationship in its state-like form (Safran et al., 2011; Safran et al., 2009), have limited time to unfold in single- or dual-session PAT. Although here, too, the intensity of the psychedelic experience might provide a space for comparable relational dynamics to occur on a temporally condensed scale. Indeed, experiences of defensiveness, suspiciousness, or mistrust towards guides or therapists, sometimes including paranoid ideation, are not uncommon in qualitative accounts of supervised psychedelic sessions (He, 2024; Koslowski & Gasser, 2024) and warrant further study to generate a more comprehensive understanding of the psychedelically altered therapeutic relationship.

While this study has provided some first empirical evidence for therapeutic alliance constituting a mechanistic factor in PAT, in line with other psychotherapeutic interventions, it remains less clear whether certain relational processes are unique to or uniquely amplified by psychedelic sessions, compared to non-drug assisted interventions. Such an amplifying role of psychedelic experiences is suggested by at least one exploratory finding presented here, namely the prediction of post-session alliance by the intensity of acute psychedelic effects, specifically emotional breakthrough experiences. Future research should further explore similar associations by assessing relational processes during post-psychedelic integration sessions which have been shown to increase over the course of time in psychotherapy, such as emotional

self-disclosure (Farber, 2003) or relational depth (Di Malta et al., 2020). Controlled trials evaluating PAT directly against existing psychotherapeutic interventions, e.g., by comparing a standard course of psychotherapy to the same course, but enriched with one or more psychedelic dosing sessions, could potentially illuminate specific similarities and differences in relational processes in PAT compared to existing psychotherapies.

Crucially, by moving beyond the notion of alliance as a static predictor of outcomes, this study supports a view of therapeutic change in PAT that is co-emergent over time through relational engagement and deepening of psychedelic states. In this sense, the neuropharmacologically induced psychedelic experience cannot be comprehensively understood on account of an individual's biology or psychology alone but is co-authored by the relational field in which it unfolds – including a shared therapeutic intentionality, expectations, and emotional history of patient and therapists. By creating a relational container that supports emotional vulnerability, openness to surrender, and tolerance of uncertainty, alliance could be understood as a scaffold that steers the psychedelic-induced destabilization of perceptual and cognitive-emotional processing patterns into the revision of maladaptive priors, as hypothesized by REBUS (Carhart-Harris & Friston, 2019), facilitating transformative mental states (Scheidegger, 2021b) that allow for beneficial pivots towards novel and adaptive patterns of thinking and behaviour (Brouwer & Carhart-Harris, 2020). Mechanistically, this view evokes conceptions of psychotherapy by which the therapeutic relationship serves to facilitate corrective emotional experiences (Christian et al., 2012), first developed in the context of psychoanalytic counselling (Alexander, 1980), and hypothesized to underlie MDMA-assisted therapy (Luoma & Lear, 2021; Luoma et al., 2022). The idea that therapeutically intentioned relational systems, such as the psychotherapeutic dyad, can serve as a model or 'playground' for (re-)learning and adjusting interpersonal processes has been

particularly influential also in the context of group therapy, popularized through Irvin Yalom's social microcosm theory (Yalom & Leszcz, 2020), suggesting that therapy provides a condensed interpersonal arena where habitual relational patterns emerge and can be observed, understood, and reshaped through new relational experiences.

6.1.2 Communitas in Naturalistic Group Experiences

In naturalistic settings of psychedelic use, social context tends to be more multifarious than the dyadic patient-therapist relationships discussed in the previous section. Chapter 4 revealed that shared psychedelic experiences in naturalistic group settings can generate emergent intersubjective phenomena – captured in the construct of communitas – that play a similarly central role in shaping psychological outcomes. Originally coined by anthropologist Victor Turner (1969), communitas describes a transient yet powerful experience of shared humanity and collective joy that can arise in liminal, often ritualized spaces. Its role in individual and collective transformation has been discussed in the context of religious service (Austin, 1981), pilgrimage (Coleman, 2002), wilderness and nature experiences (Sharpe, 2005; Turner, 2012), music festivals and raves (Kyriakopoulos, 2021; Rill, 2006; Tramacchi, 2000), and also ayahuasca travel (Mantere, 2013). Operationalised through a novel psychometric instrument, communitas was here shown to robustly predict a range of psychological outcomes, including increased well-being, connectedness, reductions in depressive and anxious symptomatology, and increased non-physicalist epistemic and ontological positions following participation in collective psychedelic sessions.

Communitas emerged as a dynamic and context-sensitive process, unfolding within the specific temporal structure of the assessed group retreats. In line with the previous chapter, which showed how relational and intrapersonal psychology impact each other reciprocally over

the course of a multi-session psilocybin RCT, this study aimed to model psychedelic effects as embedded within a particularly structured, psychosocially enriched container, i.e. that of a psychedelic retreat. In line with the findings from Chapter 3, pre-session rapport with the group and facilitators, as well as the experience of emotional support during sessions, were predictive of intensified subjective psychedelic effects. Additionally, path analyses revealed that the influence of communitas on long-term outcomes was mediated through experiences of sharing and togetherness occurring outside the dosing psychedelic session itself and that these experiences not only mediated the effects of communitas on long-term outcomes, but also of conventional intrasubjective psychedelic effects such as mystical-type and emotional breakthrough experiences. This is important insofar as it hints towards a novel explanation as to *why* the profoundly altered states of consciousness experienced under psychedelics can be therapeutic. Specifically, this finding suggests that at least partially, the therapeutic benefits of psychedelic-induced mystical-type and emotionally cathartic states may be dependent on their being expressed, listened to, and thereby validated, interpersonally.

Indeed, qualitative research has shown that spontaneous mystical experiences can lead to distress and mental health deterioration when their interpretation becomes a struggle and preoccupation - particularly when such experiences conflict with pre-existing secular worldviews or elicit negative responses from an unreceptive social environment (Van Der Tempel & Moodley, 2020). Argryi et al. (2024) found that among 26 individuals experiencing existential distress following psychedelic experiences, the most commonly named obstacle to successful coping was ‘Lack of support and understanding from others’, with a majority of participants experiencing social isolation and other social difficulties due to feeling unable to talk about their experience. In this context, activities such as sharing circles, which typically accompany collective dosing sessions in retreat settings, could be seen as a prophylactic

practice, offering a platform for participatory sense-making (De Jaegher & Di Paolo, 2007; Fuchs & De Jaegher, 2009) that may help both with the individual attribution of meaning, and buffer against experiences of isolation and ontological shock. Additionally, the experience of non-judgemental, empathic listening - and being listened to - in a group environment, a core mechanism of peer-support and mutual aid groups (Pagano et al., 2004; Repper & Carter, 2011), might allow for relational learning that can be applied outside the social microcosm (Yalom & Leszcz, 2020) of the psychedelic retreat. Taken together with the findings of the previous chapter, these results illustrate the central role of psychosocial context and intersubjective experience for the quality of acute subjective psychedelic drug effects, as well as their long-term mental health outcomes. Viewed through the lens of an enactive biopsychosocial model of psychedelic effects, therapeutic change in both individual psychotherapeutic and collective naturalistic contexts can best be understood as emergent from a circular interplay between neurobiological processes, subjective phenomenology, and the relational structures that scaffold the experience.

Notably, the predictive role of relational components such as communitas appeared particularly relevant in older adults, where conventional measures of intrasubjective psychedelic effects lost some of their predictive power. This suggests that in older demographics, therapeutic change following collective psychedelic experiences may be less dependent on conventional psychedelic drug effects, and more so on intersubjective experiences, raising the question of whether relational and experiential mechanisms, such as emotional resonance, shared intentionality, and participatory sense-making, could be reproduced in alternative, non-pharmacological formats. Chapter 5 explored this possibility by examining a psychedelic-inspired group-based virtual reality program designed to evoke

immersive, self-transcendent, and symbolically meaningful collective experiences in a population of older adults suffering from life-threatening illness (LTI).

6.1.3 Clear Light Group VR Program

Chapter 5 extended the thesis' exploration of psychosocially enriched psychedelic interventions by investigating whether certain experiential and relational features of collective psychedelic experiences could be adapted to a non-pharmacologically mediated context. The Clear Light (CL) program was designed as a six-session group intervention for people living with LTI, combining two video-based group meetings with four VR sessions that included regular sharing rounds, guided meditation, narrative exercises, and immersive audiovisual group experiences previously shown to induce mystical-type experiences and communitas at comparable levels to psychedelic substances (Glowacki et al., 2020, 2022). The intervention thereby aimed to create a container for emotional, self-transcendent, and interpersonal processes that would invoke a felt sense of presence, sharing, and togetherness between participants, without relying on pharmacological alterations of consciousness or actual physical colocation. The results indicated significant pre–post improvements across several psychological outcomes, including reductions in depressive and anxious symptoms and increases in well-being, connectedness, and spiritual well-being.

As it ventures outside the scope of substance-induced psychedelic experiences, the relevance of the CL study to the core claim of this thesis, i.e. the centrality of psychosocial variables to psychedelic effects and their outcomes, rests partially on the phenomenological proximity between the employed numadelic VR paradigm and psychedelic experiences. While the preliminary nature of the current study and the vulnerability of the older LTI population to participant burden precluded the comprehensive measurement of subjective effects, prior

studies have compared the precursor VR intervention *Isness* to effects reported in psychedelic trials (Glowacki et al., 2020, 2022). Specifically, Glowacki et al. (2020) found that participants in the *Isness* VR experience reported scores on factors of the mystical-experience questionnaire (MEQ) that were statistically indistinguishable from seven published studies using 20-42mg of psilocybin, while being significantly higher than those in nine studies using 1-20mg of psilocybin or up to 200µg of LSD. Likewise, in their 2022 study, Glowacki et al. found scores on the ego-dissolution inventory indistinguishable from those reported by participants receiving 18mg of psilocybin and, importantly, scores on the communitas scale (COMS) 6% higher than those reported by participants in collective psychedelic sessions in the previous chapter, which was statistically significant. While qualitative approaches, such as phenomenological interviews, may be better suited to identify differences between *Isness* and psychedelic experiences, these findings demonstrate that the VR intervention underlying the here reported CL program is able to produce quantifiable intra- and intersubjective effects comparable to moderate to high doses of psychedelics.

By substituting the psychedelic substance with a previously validated non-pharmacological induction method of psychedelic-like states, and adopting an interventional design that emphasises engagement with these altered states as a relational practice, the present study, albeit only indirectly, conceptually advances the broader proposition of this thesis: within the causally interconnected mesh of biopsychosocial processes that shape the emergence of psychedelic effects and their therapeutic outcomes, the specific biological catalyst (i.e. the psychedelic substance) may ultimately be interchangeable, provided that the psychosocial framework fulfils certain parameters. In other words, within an adequate relational context, it may not matter for therapeutic outcomes whether subjective effects are caused by a psychedelic drug or another experiential perturbation. Importantly, the present findings only indirectly

support this claim, in that neither measures of subjective psychedelic-like effects, such as mystical-type experiences, nor relational variables, such as communitas or rapport were directly assessed, meaning that the mechanisms driving the observed improvements in psychological outcomes remain inferential. That said, parallels can be drawn to other experiential practices that are thought to activate some of the same salutogenic mechanisms mobilised by psychedelic substance use. For example, both mindfulness meditation (Holas & Kamińska, 2023; Scheidegger, 2021a; Zanesco et al., 2023) and holotropic breathwork (Grof et al., 2010; Puente, 2014; Uthaug et al., 2022) are commonly performed in group-based, guided formats. Although empirical research investigating the role of social factors for their outcomes remains limited, studies have begun to show that group and in-person mindfulness practice may provide benefits beyond individual (e.g., web-based) approaches (Cheese et al., 2024; Hoover et al., 2022; Mantzios & Giannou, 2014), pointing to a common psychosocially mediated pathway for therapeutically beneficial experiential interventions.

In summary, Chapters 3 and 4 demonstrated that the effects of both clinical and naturalistic psychedelic use are reciprocally shaped by psychosocial context - including dyadic and group-level dynamics - as part of a unified biopsychosocial system defined by circular causation across social, psychological, and (albeit only indirectly studied) biological domains. Chapter 5 expands on this line of evidence by showing the therapeutic effects of a novel, psychosocially enriched, but digitally mediated modality known to induce psychedelic-like states. Taken together, these findings are in support of an enactive interpretation of psychedelic effects, as proposed by Meling and Scheidegger (2023, Figure 6.1), while emphasising and empirically validating the importance of social processes for the formation of psychedelic effects.

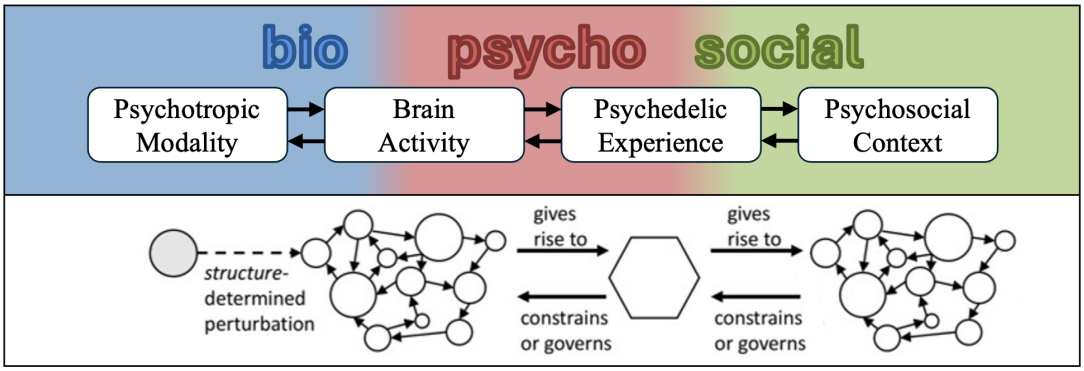


Figure 6.1 Enactive Interpretation of Psychedelic Effects after Meling & Scheidegger (2023). Psychosocial context was added as a fourth system level. Psychotropic modalities may include psychedelic substances, or non-pharmacological catalysts of psychedelic-like effects. Emphasised are the diffuse boundaries between biological, psychological and social domains. Rather than mapping 1:1 on system levels, domains may be better understood as emergent from bidirectional interactions between discreet systems: biological processes as emergent from drug-brain interactions, psychological processes from brain-experience interactions, social processes from person-environment interactions.

6.2 Clinical Implications

Human health and the practice of healing are deeply intertwined with our existence as social beings. Indeed, the practice of medicine is thought to have emerged out of the human capacities for empathy and emotional contagion, resulting in an urge to care for and heal one another - a fundamentally relational endeavour (Kohrt et al., 2020). Over time, the institutionalisation of health care, development of structured health assessments, and resulting ability to make various aspects of health quantifiable have contributed to more standardised and evidence-based approaches to care. However, with the ongoing privatization of healthcare systems, decisions about target outcomes and corresponding treatments are increasingly being driven by their cost-effectiveness, often at the expense of health equity and overall quality of care (Goodair & Reeves, 2024; Maarse, 2006; Øvretveit, 2003). Within psychiatry, this trend is exemplified by the proliferation of brief medication management visits as the default mode of patient interaction, offering fast-acting solutions over slower, relational approaches that might promise more sustainable, long-term outcomes. Psychedelic therapy has at times been portrayed as offering the best of both worlds: the potential for transformative, sustainable

change, paired with the convenience of a pharmacological intervention. In practice, however, contemporary approaches to psychedelic therapy go far beyond the administration of a drug, involving the careful curation of psychosocial and contextual parameters to maximise the likelihood of positive outcomes. The present research demonstrates that such considerations are not merely vestiges of earlier therapeutic traditions but constitute mechanistic contributors to treatment efficacy. In this way, it empirically confirms the widely held assumption that psychosocial support, before, during, and after drug administration, is critical to the success of psychedelic-assisted therapies. This support may manifest through dyadic therapeutic relationships, shared experiences within a group setting, or even in feelings of copresence in non-pharmacological psychotropic VR interventions.

What, then, are the practical implications of these findings for the therapeutic use of psychedelics? As in psychotherapy more broadly, a central mechanism for therapeutic success appears to be the establishment of a trusting relationship between practitioner and client. The present results thereby contribute to closing a critical knowledge gap that has led some to question whether a psychotherapeutic framework is truly necessary for the efficacy of psychedelic therapy (Goodwin et al., 2024). Accordingly, they substantiate concerns that insufficient psychosocial support may constitute a growing risk in clinical psychedelic use (Schenberg et al., 2024) in the face of trends towards pharmaceuticalisation and a potential "race to the bottom" in care provision. Minimizing the psychosocial components of psychedelic therapy might be attractive insofar as it could lower costs and simplify approval processes by situating psychedelic therapy more neatly within the purview of regulatory bodies such as the US Food and Drug Administration (FDA), which are not equipped to evaluate behavioural interventions. However, the findings of the present thesis suggest that such compromises are likely to diminish the efficacy of psychedelic-assisted treatments. On the contrary, rather than diminishing psychotherapeutic contact and focusing exclusively on substance administration

sessions, a more beneficial approach may involve embedding psychedelic sessions within longer-term psychotherapeutic courses, as is common in psycholytic models (Fischer, 2019; Gasser, 2022; Passie et al., 2022). Additionally, the development of manualised interventions aimed specifically at strengthening the therapeutic alliance could be valuable. While such manuals have thus far shown limited effects on depression outcomes in trials - despite improving treatment satisfaction (Michel et al., 2023) - their role may be more significant in the context of psychedelic therapy.

Given the constitutive role of language in shaping conceptual and institutional realities, careful attention should be paid to the semantic framing of psychedelic treatments. If current treatment models, all of which have included extensive psychosocial components (Carhart-Harris et al., 2016; Chisamore et al., 2024; Guss et al., 2020; Johnson et al., 2008; Kirlić et al., 2025; Raison et al., 2023; Richards, 2017; Watts, 2021), were to be framed, and ultimately approved as pharmacotherapies, this might lead to the deregulation or neglect of psychosocial support, the minimization of relational components, and ultimately, poorer outcomes for patients. By contrast, framing these interventions as psychedelic-*assisted* psychotherapy seems to circumvent such risks (Gründer et al., 2024). While such categorical heterogeneity may seem problematic from a regulatory standpoint, it has been argued that ensuring the safety and efficacy of psychedelic therapy should not come at the cost of conforming to the limitations of existing regulatory frameworks. Instead, regulatory bodies such as the FDA may need to evolve in response to innovation (Roseman, 2024). Realistically, even without such institutional restructuring, regulatory approvals are likely to result in a broad expansion of off-label prescribing and a proliferation of real-world treatment models characterized by differing levels and types of psychosocial support – for better or worse (Wexler & Sisti, 2022).

Regarding the question of whether psychedelic therapy should categorically be classified as a form of psychotherapy: While this thesis underscores the mechanistic importance of psychosocial factors for psychedelic effects, a rigid adherence to definitions would likely hinder both scientific progress and clinical innovation. Rather than asserting that psychedelic therapy is or should always be considered psychotherapy, it may be more accurate to view it as a hybrid pharmaco-psychosocial intervention that can be positioned at different points along this spectrum, depending on the specific features of its implementation. While its psychosocial component entails that the common factors identified in psychotherapy (Wampold, 2015) likely also apply to psychedelic therapy, the diversity of patient populations who are thought to benefit from psychedelics could warrant a corresponding plurality of therapeutic approaches. Crucially, detailed documentation and transparent reporting of treatment protocols will be needed to assess the relative contribution of pharmacological and psychosocial components in each case. Even in models that utilize only minimal levels of interpersonal interaction, it remains advisable to measure psychosocial constructs such as therapeutic alliance and rapport, considering that they have been shown to predict treatment response even in SSRI medication-management settings (Krupnick et al., 2006).

Ultimately, it is likely that different models of psychedelic therapy will continue to emerge, some more and some less reliant on psychosocial enrichment and psychotherapeutic intervention. Even now, differing therapeutic models are in clinical use, though they are vastly outnumbered by the diversity of approaches to psychedelic use in real-world contexts, ranging from underground facilitation to the ceremonial practices of traditional and neoshamanic settings. The influence of these informal paradigms on current clinical practice cannot be overstated and their systematic study can only be hoped to continue informing and enhancing future institutionalized medical settings. For example, the findings presented in Chapter 4,

demonstrating that group-level intersubjective experiences can contribute to the salutogenic effects of psychedelic use, highlight the added therapeutic value of group-based approaches to psychedelic administration. At the other end of the spectrum lie highly pharmacologically focused models, which in contemporary clinical application remain mostly experimental or hypothetical. Proposed examples include administration of classic psychedelics under general anaesthesia, or after pretreatment with 5-HT2A antagonists such as ketanserin, diminishing subjective effects. Such approaches could greatly reduce or eliminate the need for behavioural monitoring or psychotherapeutic engagement during dosing sessions, instead leveraging primarily neurobiological processes. While the effectiveness of such methods is unlikely to surpass psychosocially enriched psychedelic therapy, they may have unique applicability for patient populations in which unstable behavioural responses are anticipated or would be difficult to manage.

In sum, the findings presented across this thesis underscore the indispensable role of psychosocial context in shaping the outcomes of psychedelic treatments. Rather than fitting neatly into preexisting regulatory or disciplinary categories, psychedelic therapy emerges as a paradigmatically hybrid intervention - one whose efficacy is contingent on both pharmacological and relational factors. Recognizing this complexity has profound implications for how such treatments are developed, delivered, and evaluated, highlighting the utility of transdisciplinary frameworks such as the BPSM. Yet, these conclusions must be weighed in view of the study limitations, which are addressed in the following section.

6.3 Limitations and Future Directions

The findings and interpretations presented in this thesis are shaped by the particular methodological and conceptual parameters of the applied research process, each of which

introduce specific limitations that warrant critical reflection and may chart paths for future inquiry. While study-specific limitations have been discussed in each individual chapter, the following section will outline some overarching limitations by first analysing methodological, followed by conceptual constraints spanning across the present body of work.

6.3.1 Methodological Limitations

Limitations due to measurements. Across the three studies reported in this thesis, a fundamental methodological limitation lies in the exclusive reliance on psychometric self-report questionnaires as assessment tools. While the specific shortcomings of self-report questionnaires and proposed alternatives are discussed in more detail below, it must be acknowledged that this constraint stands in tension with the conceptual breadth of the biopsychosocial framework adopted for interpreting the findings. While self-report questionnaires are a well-validated and robust tool in the assessment of subjective psychological constructs, such as mental well-being, depressive symptoms, or psychedelic phenomenology, and to a lesser extent for social constructs, such as therapeutic alliance or group cohesiveness, any claims regarding biological processes made in this thesis remain necessarily inferential, grounded in the existing literature on physiological correlates of psychedelic effects, rather than in direct empirical assessment. As such, the biopsychosocial model (BPSM) invoked in the introductory and discussion sections should be regarded not as an empirically triangulated account, but as a broader interpretative scaffold chosen to conceptually anchor the psychosocial focus of this research within the biological dimension of the studied interventions.

Beginning to unpack the specific limitations of self-report questionnaires in the context of this research, a first issue lies in their questionable ability to capture the complex phenomenology of psychedelically altered states of consciousness. Empirically, this issue is captured for example by a lack of differentiation between different types of psychedelic substances. Linguistic analyses of narrative drug experience reports clearly suggest that significant differences exist in the phenomenology of different psychedelic drugs (Ballentine et al., 2022; Hase et al., 2022; Noah et al., 2024; Zamberlan et al., 2018). However, psychometrically validated self-report questionnaires have thus far struggled to demonstrate substance-specific differences (Holze et al., 2022; Holze et al., 2020; Ley et al., 2023; Shinozuka et al., 2024), suggesting a need for more granular assessments, and the potential value of qualitative data and mixed-method approaches. The inability of psychometric questionnaires to provide a comprehensive account of psychedelic phenomenology is particularly problematic for the interpretation of findings by Glowacki et al. (2020, 2022) that were premising the relevance of the VR-based experience discussed in Chapter 5 as a psychedelic-adjacent intervention. In this case especially, but also for gaining a more comprehensive insight into dyadic (Chapter 3) and group-level (Chapter 4) psychedelic intersubjectivity, the collection of qualitative data could be extremely valuable in future studies. Interview-based approaches such as microphenomenology (Sanders et al., 2024), thematic analysis using grounded theory (Roseman et al., 2021), and computational analysis of natural language (Cox et al., 2021; Tagliazucchi, 2022) have all been applied successfully in the context of psychedelic research, in one case already with a focus on relational dynamics (Roseman et al., 2021).

Beyond the lack of granularity offered by psychometric questionnaires assessing psychedelic phenomenology, the individual self-report approach can also be considered

lacking given the present research focus on intersubjective effects. Future studies could benefit from utilizing multi-perspectival assessments by including also therapist-, facilitator-, or observer-rated measures of therapeutic alliance, such as the video-based measure of therapeutic connection validated by Gramling et al. (2023). Group level intersubjective effects like communitas could furthermore be analysed across multiple participants within the same retreat or group session, exploring whether inter-participant correlations or compound scores might similarly predict long-term psychological outcomes. In the same vein, the observed changes in well-being, depression, social connection, and other long-term outcomes reported across the three studies, could all lend themselves to conventional clinician-based ratings, or perhaps even more fittingly, ratings from multiple informants from among the participants' peers, which can provide a more context-oriented insight into a subject's mental and social health (Alexander et al., 2017).

Lastly, a wide array of physiological assessment methods could allow future research to investigate biological processes underpinning the psychosocial effects of psychedelics, thereby addressing a major gap of the present thesis, considering its conceptual framing within the BPSM. Interpersonal physiological synchrony has long been indicated as a biomarker of dyadic relationships, including in psychotherapy (Koole & Tschacher, 2016), with a number of studies showing patient-therapist concordance in electrodermal activity (Marci et al., 2007), heart rate (Gernert et al., 2024), respiration (Tschacher & Meier, 2020), and neural activity via EEG, fMRI, and fNIRS (Adel et al., 2012) to be predictive of subjective ratings of therapeutic alliance and also therapy outcomes. Similarly, studies of group activity both under experimental conditions (Gordon et al., 2020; Tomashin et al., 2022) and during naturalistic collective events (Baranowski-Pinto et al., 2022; Konvalinka et al., 2011) have shown measures of physiological synchrony to predict experience of greater group cohesion and initial

research has found evidence for synchrony-mediated increases of empathy and social presence ratings in multiagent VR environments (Järvelä et al., 2021; Salminen et al., 2019). Accordingly, simultaneous assessment of peripheral physiological markers through unintrusive wearables during preparation, dosing, and integration sessions in psychedelic therapy, naturalistic psychedelic ceremonies, or during group VR sessions could potentially provide a fascinating window into processes of interpersonal synchronization involved in altered states of consciousness. Together with the potential for hyperscanning neuroimaging techniques applied during psychedelic sessions (Scholkmann & Vollenweider, 2023), such assessment techniques, combined with rigorous, multi-perspectival psychometric and qualitative assessments, could enable future work to model the circular causal dynamics between neurophysiological and relational processes, advancing a truly biopsychosocial understanding of both the acute and long-term effects of psychedelics and related experiential modalities.

Statistical limitations. While most statistical assumptions of the used analysis techniques were either controlled for or accounted for by means of robust estimation methods, the path analyses included in Chapters 3 and 4 included several single-item instruments, for which internal consistency values cannot be calculated. Thus, these items introduced an uncontrolled amount of measurement error into the models, which is especially problematic in more complex models, i.e. models with a large number of estimable parameters (Cole & Preacher, 2014). Future studies could avoid this caveat by using longer, validated assessment tools for constructs such as identity fusion, rapport, or in-session emotional support, or by using analyses that are robust to measurement error, such as structural equation modelling with latent variables.

The temporally sparse structure of the collected behavioural data only allowed for very basic tests of reciprocal relationships between constructs. In order to better statistically approximate the idea of circularity as suggested by enactive accounts of biopsychosocial causation, longer and higher density time series data would be required, allowing for more advanced statistical tools to be applied. For example, the use of brief ecological momentary assessments of intra- and intersubjective phenomenology across dosing sessions could provide temporally rich behavioural subjective data, while observer ratings (e.g., of therapeutic interactions) or peripheral physiological biomarkers represent assessment methods that could be employed with minimal interruptions to the flow of the experience. Depending on the temporal and feature density of the resulting data, as well as specific hypotheses, time series techniques such as dynamic structural equation modelling (Asparouhov et al., 2018), vector autoregression (Kilian & Lütkepohl, 2017) or Granger causality analysis (Angelini et al., 2009; Granger, 1969) could all be suitable for investigating circular relationships between assessed variables.

Finally, study designs employing targeted experimental manipulations of the psychosocial container of psychedelic administration will be necessary to strengthen the claims of causality made here. For example, 2x2 factorial studies removing or downregulating psychological support (e.g., by reducing preparatory and integration activities or administering the substance without therapists present in the room) or upregulating psychological support (e.g., by integrating psychedelic sessions within a long-term psychotherapy course) may be helpful to identify respective contributions and interactions of pharmacological and psychosocial mechanisms.

6.3.2 Conceptual Limitations

The present thesis was framed within the biopsychosocial model (BPSM) and informed by enactive cognitive science, frameworks that carry important conceptual limitations meriting reflection. Originally developed to counter representationalist models of cognition, enactivism emphasises the dynamic, embodied, and relational processes through which mind and world co-emerge via structural coupling between organism and environment (Varela et al., 2017). However, the notion of circular causality, central to this framework, was conceived in the context of continuous, moment-to-moment feedback loops within real-time sensorimotor engagements, rather than temporally discrete psychological events measured days or weeks apart. Its application to the present results - e.g., in interpreting bidirectional influences between therapeutic alliance measured a day before and subjective psychedelic effects during a psychedelic session - thus extends the term beyond its original scope as a new form of phenomenologically grounded cognitive science. While such uses may be defensible in the context of complex systems theory, they risk diluting the conceptual boundaries of enactivism by reducing embodied interaction to covariance of variables across lagged timepoints. That said, enactivist principles of structural coupling and co-emergence have been discussed on a variety of spatial and temporal scales, emphasising a continuity from human and non-human to minimal (e.g., single-cell) cognition (Maturana & Varela, 2012) and within biosemiotic enactivism (De Jesus, 2016), even to biomolecular processes (Meacham, 2016). Towards slower and larger scales, ideas of enactive organism-environment coupling have been applied to developmental biology (Colditz, 2020), genetics (Meloni & Reynolds, 2021), and natural species drift in evolutionary biology (Varela et al., 2017). While the present operationalizations remain crude applications of organism-environment coupling, they are therefore hoped to draw attention to the transdisciplinary utility of enactivist principles in the context of biopsychosocially complex interventions such as psychedelic therapy.

In its application to psychiatry, enactivism has sometimes been cast as a necessary corrective for a long-recognized (e.g., Molina, 1984) shortcoming of the BPSM, namely its inability to adequately explain how biological, psychological, and social processes interact in a causally integrated manner (De Haan, 2020a, 2020b, 2021). Indeed, the tripartite structure of the BPSM, appearing to neatly separate the world into biological, psychological, and social processes - as attempted in the introductory chapter of this thesis - has been criticised for artificially generating distinctions between its domains (Cabaniss et al., 2015; Tavakoli, 2009) offering no means for integration. While thereby enabling various disciplines to claim validity and mechanistic relevance, Ghaemi (2009, 2011) argued that this was achieved at the cost of eclecticism, leading to irredeemable vagueness and incoherence. A defence of Engel's original description of the BPSM, however, highlights its grounding in Bertalanffy's (1968) general systems theory, which does provide a conceptual framework for inter-level interactions. Like enactivism, general systems theory departs from linear notions of causation, positing instead that causes and effects emerge through recursive, circular feedback loops (Tramonti et al., 2019). This shared emphasis on dynamic recursivity shows the conceptual proximity between the BPSM and the enactive approach and is the reason why the present thesis adopts an integrative stance, drawing on enactivist thought to inform a philosophically grounded and phenomenologically attuned modernization of the BPSM (Cormack et al., 2023).

It is important to recognize that the BPSM was never intended to function as a scientific model in the narrow sense of generating directly testable hypotheses. Rather, it represents a framework for organizing clinical reasoning and guiding the broader academic discipline of medicine. Its core utility lies in orienting the attention of researchers, clinicians, and regulators toward the complex interdependence of causal systems that shape human health. Despite

longstanding ideological and conceptual divides, the BPSM continues to serve as a foundational paradigm in academic psychiatry, informing the structure of most residency-training programs as what has been called the quiet ‘solid center’ of psychiatric practice (Pies, 2016). For psychedelic research - a field that tends to oscillate between radical innovation and speculative idealism - positioning itself within this center might offer both a stabilizing anchor and a productive counterbalance to tendencies toward exceptionalism. Grounding psychedelic science in the integrative ethos of an enactive BPSM could thus not only facilitate interdisciplinary collaboration but also encourage the development of clinically relevant research questions and safeguards for best practices in care.

6.4 Conclusion

The present research has highlighted the dynamic, constitutive role of psychosocial factors for psychedelic effects across clinical, naturalistic, and digitally mediated contexts. Drawing on evidence from a randomized controlled trial and large-scale observational cohort studies, the findings support a view of long-term therapeutic outcomes as co-emergent from recursive bio-psycho-social feedback loops - linking psychotropic catalysts, intrasubjective phenomenology, and relational context. This confirms long-standing assumptions about the importance of psychosocial structures containing psychedelic experiences and underscores clinical and epistemic risks inherent to biomedical reductionist framings of psychedelics.

By definition, psychedelic experiences are thought to be mind-revealing. Yet, depending on our interpretative frameworks, we might come to different conclusions about the nature of said mind. Here, a view is taken that conceives of the brain, rather than being a reducing valve of incoming information, as a mediating organ for dynamic, reciprocal relationships between the organism and its environment (Fuchs, 2011). In this perspective, both

mind and brain are fundamentally relational in function, experience itself a mode of being-in-relation. The deeply felt sense of interconnectedness, often associated with psychedelics, may speak to their capacity to uncover this fundamental relationality of existence. Much might be gained if we were able to extend this insight outward, toward the collective structures of institutional health care and society at large (Forstmann & Sagioglou, 2025). By encouraging us to cultivate nourishing social containers to support therapeutically meaningful experiences, psychedelics may, in turn, remind us that thoughtful, compassionate human connection is not ancillary to healing—it is its very medium.

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Appendices

Appendix A: Measures

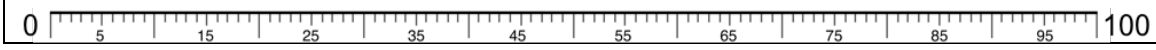
A1: Rapport (PPS) (Angyus et al., 2024)

Please read each statement below and use the relevant scale to indicate how you feel right now, in this present moment. If you wish to leave the slider in the starting position, please be sure to still click the slider or the response will not be registered, which will prevent you from moving on to the next page. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to best describe your present feelings.

I have a good feeling about my relationship with the group/people who will be with me during my experience.[2]



I have a good relationship with the main person/people who will look after me during the upcoming experience.[1, 2]



[1] Item used to assess rapport in Chapter 3; [2]Items used to assess rapport in Chapter 4

A2: Emotional Support

On a scale between 0 (Not at all) and 100 (Most imaginable), to what extent did the following elements influence the overall quality of your experience? If an element was not present during your experience, you can just leave the field blank.

Emotionally supportive individual(s)



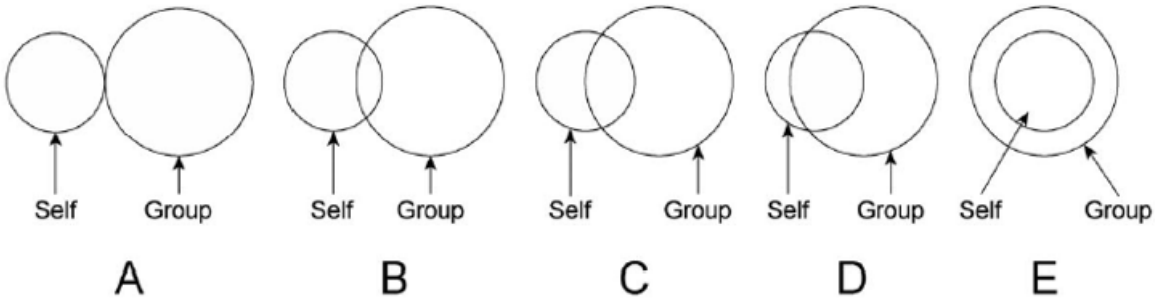
A3: Communitas Scale (COMS) (Kettner et al., 2021)

Please indicate how strongly you agree or disagree with the following **statements about your past experience**, taking into account that 1=Strongly disagree and 7= Strongly agree.

1 = Strongly disagree, 2 = Disagree, 3 = Somewhat disagree, 4 = Neither agree nor disagree, 5 = Somewhat agree, 6 = Agree, 7 = Strongly agree							
During the ceremony, I felt a bond with my fellow participants that I could not experience outside the ceremony.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, I felt a sense of belonging with the other participants.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, I felt a sense of harmony with the others.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, I felt a sense of sharing with the other participants.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
The ceremony really allowed me to get to know the other participants.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, I felt that social status became irrelevant.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, I experienced all participants as equal based on basic shared humanity.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, ego-related tensions between participants seemed to resolve.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, I felt a strong connection to another participant.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
During the ceremony, I felt a strong connection the facilitator or shaman.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Note. For the post-retreat version of the questionnaire, each instance of 'ceremony' is replaced with 'retreat'. *Items are not part of the main scale and analysed separately.							

A4: Pictographic Identity Fusion Scale (Gómez et al., 2011)

Please have a look at the picture below and indicate the letter of the image that represents best how you feel in relation to the ceremony group **at this moment**.



Adapted from: Gómez, A., Brooks, M. L., Buhrmester, M. D., Vázquez, A., Jetten, J., & Swann Jr, W. B. (2011). On the nature of identity fusion: insights into the construct and a new measure. Journal of personality and social psychology, 100(5), 918.

A5: Revised Self-Disclosure Scale (RSDS) (Wheeless & Grotz, 1976)

Please mark the following statements to reflect **how you communicated with other people** over the course of the past retreat (from the moment when you arrived at the ceremony location to the moment when you left it), **including one-to-one conversations and sharing-circles**. Note that 1=Strongly disagree and 7= Strongly agree

1 = Strongly disagree, 2 = Disagree, 3 = Somewhat disagree, 4 = Neither agree nor disagree, 5 = Somewhat agree, 6 = Agree, 7 = Strongly agree							
When I wished, my self-disclosure was an accurate reflection of who I really am.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
When I expressed my personal feelings, I was always aware of what I was doing and saying.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
When I revealed my feelings about myself, I consciously intended to do so.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I did not often talk about myself.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
My statements of my feelings were usually brief.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
My conversations lasted the least time when I was discussing myself.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Only infrequently did I express my personal beliefs and opinions.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I usually disclosed positive things about myself.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
On the whole, my disclosures about myself were more negative than positive.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I could not reveal myself when I wanted because I did not know myself thoroughly enough.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I was often not confident that my expressions of my own feelings, emotions, and experiences were true reflections of myself.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I was not always honest in my self-disclosures.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I did not always feel completely sincere when I revealed my own feelings, emotions, behaviors, or experiences.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I intimately disclosed who I really am, openly and fully in my conversations.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Once I got started, my self-disclosures lasted a long time.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
I typically revealed information about myself without intending to.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
My messages revealed mostly what I like.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
My disclosures of personal beliefs and opinions were always directly related to the conversation.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
*Items are reverse-coded							

From: Wheeless, L. R., & Grotz, J. (1976). Conceptualization and measurement of reported self-disclosure. Human communication research, 2(4), 338-346.

A6: Metaphysical Beliefs Questionnaire (MBQ) (Timmermann et al., 2021)

You will be presented with a series of statements about the nature of consciousness and reality. Please read each statement carefully and rate the extent to which you agree or disagree with each item using the following scale'

1 = Strongly disagree, 2 = Disagree, 3 = Somewhat disagree, 4 = Neither agree nor disagree, 5 = Somewhat agree, 6 = Agree, 7 = Strongly agree							
There exists another separate realm or dimension beyond this physical world that can be experienced or visited.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visiting such immersive "realms" or "worlds" can sometimes depend on a supernatural / magical transition process or event.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
There are two separate realms of existence, the physical (body, brain and external world) and the mind, the latter being non-physical/non-material.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
There is just one primary reality: the mind and/or consciousness and all material things derive from it.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
There is just one primary reality: the physical; the mind (and/or consciousness) is just physical/functional properties of the brain and has an entirely material explanation.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
There are other realms of existence which are more important than everyday reality.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
The universe obeys a unifying principle which is beyond any possible material or scientific explanation.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
The universe obeys a unifying principle which is (in theory) completely addressed by a material or scientific explanation.*	**1**	**2**	**3**	**4**	**5**	**6**	**7**
The physical world is an illusion generated by consciousness or the mind.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Mind, consciousness, or soul is a fundamental quality of all things in the universe, either animate or inanimate.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
My conscious experience is entirely a construction of reality performed by my brain. (Internalism about consciousness)	**1**	**2**	**3**	**4**	**5**	**6**	**7**
My 'self' is entirely a construction of my brain.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
My experience and my 'self' are deeply rooted in my body and its interactions with the world and not the sole construction of my brain.	**1**	**2**	**3**	**4**	**5**	**6**	**7**

*Note. Only items in **bold** are included in the main factor (non-physicalist beliefs. *Items are reverse-coded.*

A7: Watts Connectedness Scale (WCS) (Watts et al., 2022)

Reflecting on how you have felt over the past 2 weeks, please rate the following items on a scale from **'Not at all' to 'Entirely'** according to how you have felt over this time period. Please answer every item, even if you are unsure or feel the item is unclear or poorly worded. Drag the indicator to a position on the scale that shows how much you agree or disagree with each of the following statements.

Each item is rated on a 0 – 100 visual analogue scale with the anchors 0 = Not at all, 100 = Entirely



1.	I have felt trapped in my mind.*
2.	My mind has felt connected to my heart/emotion.
3.	I have felt connected to my senses (touch, taste, sight smell, hearing).
4.	I have felt connected to a range of emotions.
5.	If I had chosen to, I could have 'sat with' painful memories.
6.	I have felt connected to my body.
7.	I have been able to fully experience emotion, whether positive or negative.
8.	I have felt alone.*
9.	I have felt connected to friends and/or family.
10.	I have felt connected to a community.
11.	I have felt connected to all humanity.
12.	I have felt unwelcome amongst others.*
13.	I have felt separate from the world around me.*
14.	I have felt connected to a purpose in life.
15.	I have felt connected to nature.
16.	I have felt connected to a spiritual essence (in the secular or religious sense).
17.	I have felt connected to a source of universal love.
18.	I have seen things from a broad perspective, 'the bigger picture'.
19.	I have felt that everything is interconnected.

**Items are reverse-coded.*

Appendix B: Diagnostic and Supplementary Statistical Information

This Appendix includes detailed diagnostics and model output supporting each results chapter.

B1: Chapter 3: Therapeutic Alliance Study

Path Analysis Diagnostics.

Table A3.1: Diagnostics for confirmatory path analyses

	EBI_{Max}	MEQ_{Max}
Multivariate normality		
Mardia Skewness	**72.2 (.0002)**	**94.1 (<.0001)**
Mardia Kurtosis	**2.1 (.034)**	**3.0 (.003)**
Homoscedasticity		
Breusch-Pagan Test (Max)	**17.4 (.002)**	6.7 (.15)
Linearity		
Harvey-Collier Test (Max)	0.14 (.89)	0.05 (.96)
Multicollinearity (VIF_{Max})	1.43	1.56

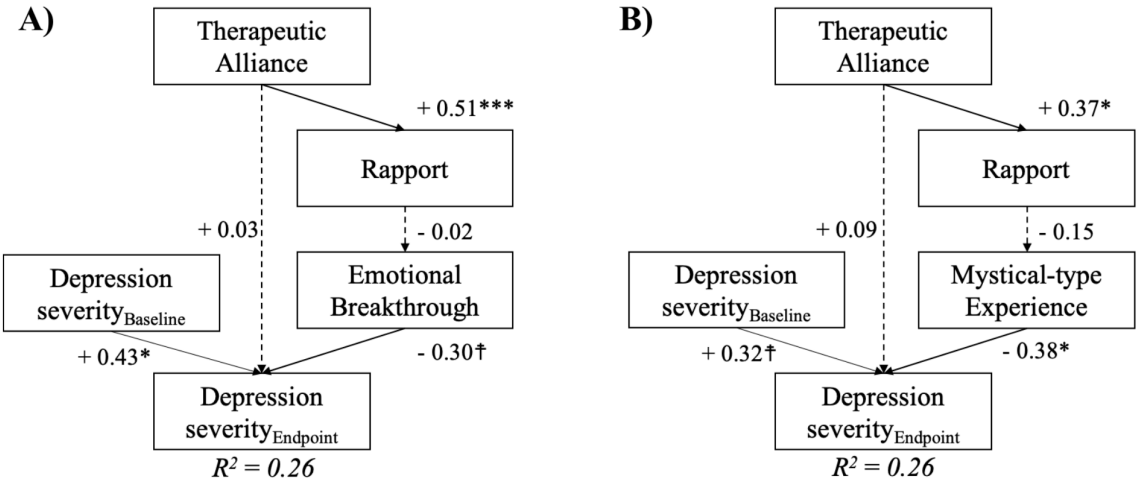
*Note. Significant violations of assumptions in **bold**. Only the most significant results for Breusch-Pagan and Harvey-Collier Tests are reported in case of multiple dependent variables. EBI: Model including Emotional Breakthrough Inventory; MEQ: Model including Mystical Experience Questionnaire*

Table A3.2: Diagnostics for exploratory path analyses

	EBI_{DD1}	MEQ_{DD1}	EBI_{DD2}	MEQ_{DD2}
Multivariate normality				
Mardia Skewness	61.0 (.30)	63.9 (.21)	**56.3 (.013)**	**55.5 (.015)**
Mardia Kurtosis	-0.4 (.69)	-0.26 (.80)	1.42 (.15)	1.01 (.31)
Homoscedasticity				
Breusch-Pagan Test (Max)	**11.1 (.025)**	6.66 (.16)	6.84 (.14)	7.81 (.05)
Linearity				
Harvey-Collier Test (Max)	0.52 (.61)	1.32 (.20)		0.29 (.77)
Multicollinearity (VIF_{Max})	1.78	1.68	2.15	2.06

*Note. Significant violations of assumptions in **bold** Only the most significant results for Breusch-Pagan and Harvey-Collier Tests are reported in case of multiple dependent variables. DD: Dosing Day; EBI: Model including Emotional Breakthrough Inventory; MEQ: Model including Mystical Experience Questionnaire*

Confirmatory path analysis results for the escitalopram arm

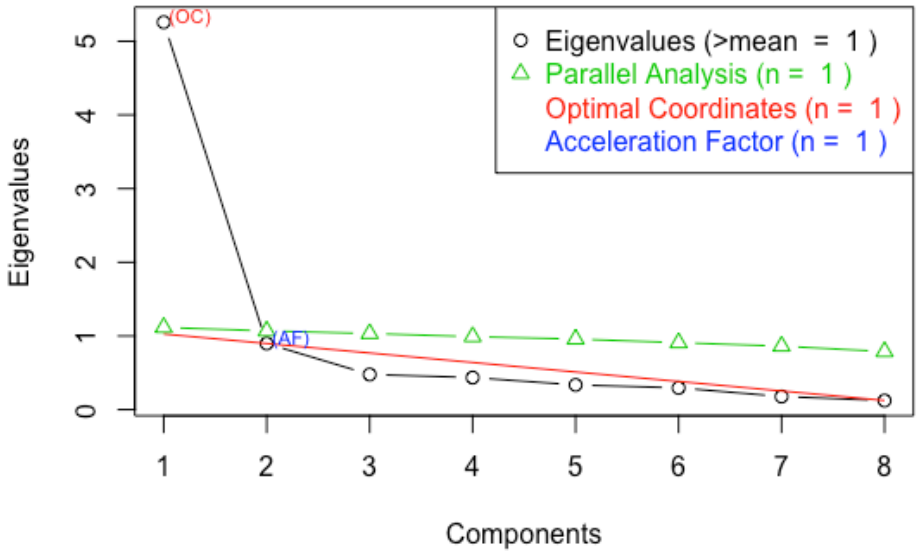


Supplementary Figure A3.1. Path models testing whether therapeutic alliance would lead to better depression scores 6 weeks following the 1mg psilocybin dose administered in the Escitalopram arm of trial. Serial mediation of therapeutic alliance via pre-session rapport and A) Emotional Breakthrough and B) Mystical-type Experiences were not supported by the models, even though acute experience scores still showed trend level significant effects on outcomes. Depression severity at the 6-week Endpoint was adjusted for baseline depression scores - which by itself accounted for R2 = 0.17, i.e. 17% of variance in the final outcome (value not shown in the above models). This means that when this amount of variance was removed, the EBI and MEQ models explained 26% -17% = 9% of variance in final depression scores. Numbers represent standardised regression coefficients for significant (solid) and non-significant (dashed) paths. In comparison, the equivalent path models for 25mg psilocybin the EBI-based model explained 42% - 12% = 30% and the MEQ-based model explained 32% - 12% = 20% of variance in depression severity at the key endpoint. Reproduced with permission from Murphy et al. (2022).

† indicates $p < .1$, * $p < .05$, *** $p < .001$

B2. Chapter 4: Communitas Scale Validation

Communitas Scale factor number determination



Supplementary Figure A4.1 Scree plot displaying eigenvalues and results of non-graphical tests to determine optimal number of factors to retain in the adapted Communitas Scale (COMS). Internal consistency of this single factor solution was excellent with Cronbach's alpha = 0.92. This figure has been reproduced with permission from Kettner et al. (2021).

Path analysis diagnostics

Table A4.1: Diagnostics for all included path analyses

	COMS	MEQ	EBI	MBQ
Multivariate normality				
Mardia Skewness	**566.2 (<.0001)**	**556.6 (<.0001)**	**569. (<.0001)**	**157.14 (.013)**
Mardia Kurtosis	**7.3 (<.0001)**	**7.2 (<.0001)**	**7.5 (<.0001)**	**-0.20 (.84)**
Homoscedasticity				
Breusch-Pagan Test (Max)	**39.2 (<.0001)**	**33.9 (<.0001)**	**38.7 (<.0001)**	6.7 (.15)
Linearity				
Harvey-Collier Test (Max)	0.98 (.32)	0.93 (.35)	0.92 (.36)	1.27 (.21)
Multicollinearity (VIF_{Max})	1.16	1.14	1.05	1.13

Note. Significant violations of assumptions in ***bold****. Only the most significant results for Breusch-Pagan and Harvey-Collier Tests are reported in case of multiple dependent variables. COMS: Model including Communitas Scale; EBI: Model including Emotional Breakthrough Inventory; MBQ: Model predicting changes in non-physicalist beliefs assessed via the Metaphysical Belief Questionnaire; MEQ: Model including Mystical Experience Questionnaire*