Review

‘Psychedelic’ as Mind-Revealing: Psychological Processes in the Subjective Experience That Drive Positive Change

Rúna F. E. Walther * and Hein T. van Schie

Posted Date: 30 July 2024

doi: 10.20944/preprints202407.2400.v1

Keywords: psychedelic; altered states of consciousness; therapeutic change; psychedelic-assisted therapy; psychology; mental health

Review

'Psychedelic' as Mind-Revealing: Psychological Processes in the Subjective Experience That Drive Positive Change

Rúna F. E. Walther [1,*] and Hein T. van Schie [2]

[1] Radboud University, School of Psychology, Nijmegen, The Netherlands; runa.walther@gmail.com
[2] Radboud University, Behavioral Science Institute, Nijmegen, The Netherlands; hein.vanschie@ru.nl
* Correspondence: runa.walther@gmail.com

Abstract: This narrative review explores the utilization of psychedelic states in therapeutic contexts, deliberately shifting the focus from psychedelic *substances* back to the *experiential phenomena* they induce, in alignment with the original meaning of the term "mind-manifesting." The review provides an overview of various psychedelic substances used in modern therapeutic settings and ritualistic indigenous contexts, as well as non-pharmacological methods that can arguably induce psychedelic states, including breathwork, meditation, and sensory deprivation. While the occurrence of mystical experiences in psychedelic states seems to be the strongest predictor of positive outcomes, the literature of the field yields several other psychological processes, such as awe, perspective shifts, insight, emotional breakthrough, acceptance, re-experiencing of memories, and certain aspects of challenging experiences, that are significantly associated with positive change. We additionally discuss in detail mystical experience related changes in metaphysical as well as self-related beliefs and their respective contributions to observed outcomes. We conclude that a purely medical and neurobiological perspective on psychological health is reductive and should not overshadow the significance of phenomenological experiences in understanding and treating psychological issues that manifest in subjective realities of human individuals.

Keywords: psychedelic; altered states of consciousness; therapeutic change; psychedelic-assisted therapy; psychology; mental health

1. Introduction

Utilization of Altered States of Consciousness (ASCs) for therapeutic purposes can be traced back to prehistoric civilizations. Substances like psilocybin and ayahuasca have historically been, and still are, central to healing rituals and regarded as sacred in indigenous societies across the globe and across time [1–3]. Recent years have seen a surge of interest into the therapeutic potential of psychedelic and related substances as evidence of their effectiveness in treating various mental health conditions has amounted [4,5]. For example, psilocybin shows promising therapeutic efficacy for treatment of mood disorders [6–12], substance addiction [13], and end-of-life anxiety, among others [3]. The dissociative ketamine is increasingly tested and was recently approved for treatment-resistant depression [14], and the US Food and Drug Administration (FDA) has designated MDMA-assisted psychotherapy as a "Breakthrough Therapy" in 2017. Additionally, research on indigenous plant medicines, like ayahuasca and mescaline, and their effects are being researched within and outside of their original cultural contexts [15–20] .

Psychedelic states can be utilized as a means to achieve therapeutic objectives [1,3] in a variety of ways. Apart from neurobiological mechanisms, the literature on psychedelic-assisted psychotherapy proposes several mechanisms and psychological processes within acute psychedelic experiences that are associated with subsequent clinical improvement [2,14,21–26]. This review intends to provide an overview of various psychedelic substances used in modern therapeutic settings and ritualistic indigenous contexts, as well as non-pharmacological methods that induce

 doi:10.20944/preprints202407.2400.v1

psychedelic states, and particularly these states' inherent subjectively experienced psychological processes that are associated with positive change.

We thereby aim to contribute to the scientific understanding of the processes that drive therapeutic change, which may assist in the development of specific frameworks for more increasingly targeted and effective therapeutic interventions that are able to optimally harness psychedelic states for clinical outcomes [22]. Insight into how change occurs aids in identifying the clients or patients who are most likely to derive significant value from these kinds of therapy and experiences, and, by considering contextual factors of, for example, particular therapeutic approaches or ceremonial settings, the specific circumstances that are most conducive to these benefits. This additionally enhances safety and accessibility of pharmacologically-assisted therapies employing altered states of consciousness, and especially in a young and potentially still stigmatized field, facilitate conversation in the scientific and clinical community through demystification [27]. For psychotherapy in general, researchers have long noted the importance of studying change processes in their specific context (i.e., the sessions themselves), and to extend our understanding of that change beyond mere outcome measures with the ultimate goal of making therapy more effective [28].

Of all substances reviewed in this paper, classical psychedelics are currently the most extensively studied. Other substances such as ketamine and cannabis, as well as the non-pharmacological methods, have received researchers' attention partly because of the similarity of their respective phenomenology to the acute psychedelic state, while having distinct pharmacological and neurological mechanisms of action [1,3]. The review will thus include classical psychedelics like psilocybin, LSD, and DMT, as well as the substances *3,4-methylenedioxymethamphetamine* (MDMA), ketamine, and cannabis, the indigenous plant medicines ayahuasca, mescaline, and ibogaine, and additionally present non-pharmacological methods such as breathwork, meditation, and sensory deprivation before illustrating the psychological processes by which these modalities effect therapeutic change through the subjective experience of the 'psychedelic' state.

2. Psychedelic- and Substance-Assisted Therapy

Therapies utilizing pharmacologically induced psychedelic states are pooled under the umbrella terms "psychedelic-assisted therapy", more inclusively "substance-assisted psychotherapy" [3], or specifically as psilocybin-assisted psychotherapy, LSD-assisted psychotherapy, MDMA-assisted psychotherapy, or ketamine-assisted psychotherapy. In sessions involving high doses of hallucinogenic substances, it is common to use eyeshades to enable stronger focus on the internal experience, but at least two therapists or session monitors are present throughout to provide support if required. Ketamine-assisted therapy often involves minimal interactions, while for MDMA there exist more specific protocols and manuals for interventions, and LSD, psilocybin, and ibogaine studies vary along this spectrum [29].

2.1. Serotonergic Psychedelics: Psilocybin, LSD, and DMT

In 1938, the Swiss chemist Albert Hoffmann synthesized lysergic acid diethylamide (LSD), which essentially marked the beginning of psychedelics' entry to modern medicine [1]. Rapidly growing research through the 1950s contributed to the early understanding of serotonin systems and its role in cognition, and much research was conducted on clinical potential and safety of psychedelics [30,31]. The Controlled Substances Act of 1980 in the US, as well as the United Nations Convention on Psychotropic Substances in 1971 effectively illegalized psychedelic substances, and research was severely impeded until recent years [1].

Psilocybin, LSD, and N,N-Dimethyltryptamine (DMT) are considered classical serotonergic psychedelics while differing slightly in their chemical structures and subjective effects. They are currently assumed to exert their effects by binding predominantly to the 5-HT2A serotonin receptor subtype, which is presumed to lead to a cascade of effects, including downstream changes in neurotransmitter release of particularly dopamine and glutamate, and altered neuronal and functional connectivity [32]. Additionally, increased neuroplasticity is generated by cascades of neurochemical effects including the release of brain-derived neurotrophic factors (BDNF) and

 doi:10.20944/preprints202407.2400.v1

subsequent expression of genes that are related to neuroplasticity and affect protein synthesis for synaptic components [5,22,33,34]. Reduced levels of BDNF have been observed in people suffering from anxiety, depression, and addiction [35], and boosting of BDNF levels is a biological mechanism of selective serotonin reuptake inhibitors (SSRIs), which implies a role of BDNF and enhanced neuroplasticity in the therapeutic effects of psychedelics [33].

Users of serotonergic psychedelics report vivid visual hallucinations with perceptual alterations in light, sound, and touch, accompanied by changes in mood, prevalently towards joy and euphoria yet encompassing the whole emotional spectrum [36], and feelings of unity or ego dissolution which can culminate in complete mystical and deeply spiritual experiences [1,37]. Cognition can feel accelerated and hyper-associative [26], and users report abstract visions of colours and geometric patterns, sometimes also visions of creatures or places. Spontaneous personal insight is common and frequently imbued with a strong sense of meaning and significance [36,38,39]. Individual experiences often reflect personal history and symbolism [26,36,40]. The intensity and nature of these psychological effects vary widely based on factors like dosage, setting, and support [41].

Contemporary research has mainly investigated the therapeutic applications of psilocybin [6–8,42], while clinical investigations pertaining LSD and pure DMT are rarer [1]. Among outcomes of these investigations are reductions in symptoms of depression [6,8,11,43,44], reduced anxiety around death [45], reduced substance misuse [46] by mechanisms such as increased cognitive and psychological flexibility [47,48], as well as improved mental well-being, happiness, trust, empathy, positive mood, pro-sociality, (self-)acceptance, openness, mindfulness, and sense of meaning and belonging [27,40,49–51].

2.2. Other Substances: MDMA, Ketamine, and Cannabis

The entactogen MDMA also acts to increase serotonin, as well as the other monoamines norepinephrine and dopamine through reuptake inhibition and reversal of transporter proteins [52]. Through downstream serotonin effects, it additionally increases levels of cortisol, prolactin, vasopressin, and oxytocin [3], all of which predominantly lead to increased feelings of empathy (reflected by the alternative term "empathogen"), self-confidence, and sociability. Other self-reported subjective effects are increased well-being, mood, introspection, and emotional openness [53,54], but little hallucinogenic effects are reported. MDMA, like the classical serotonergic psychedelics, has been found to increase neuroplasticity through BDNF release, the effects of which are said to reinforce learning in the context of psychotherapy that accompanies the altered state experience [52].

Ketamine-assisted psychotherapy (KAP) is supported by numerous studies to be a promising therapeutic intervention for the treatment of treatment-resistant depression and substance use disorders [14]. Different frameworks for KAP exist that incorporate ketamine infusions into psychotherapeutic treatment either in-between sessions or in-sessions with lower, sub-anaesthetic doses [14]. However, ketamine is currently still primarily delivered as a standard pharmacological intervention without specific psychological assistance or psychotherapy [21] which is somewhat concerning considering its substantial psychoactive effects. It's theorized that ketamine promotes neuroplasticity through release of BDNF as well, while simultaneous cognitive-behavioural therapy supports in stabilising new synaptic connections [55].–

Interestingly, the subjective experience after consuming a high dose of cannabis has been suggested to overlap with reactions to psilocybin [56–58]. With high dosage, cannabis users report experiences of oceanic boundlessness, ego dissolution, and emotional breakthrough much alike the ones occasioned by classical psychedelics [56,57,59] and therefore might similarly act as a mediator for therapeutic outcomes here. However, clinical research is limited to one case report of 10 cannabis-assisted therapy sessions over 5 months, and reported hypothetical expectations of patients [57].

 doi:10.20944/preprints202407.2400.v1

2.3. Contextual Factors in Substance-Assisted Therapy

2.3.1. Set and Setting

The terms "set" and "setting" have become well established as crucial factors influencing trip experiences in clinical research [1,29,33] and refer to the internal disposition of the individual and the external environment in which the therapeutic session occurs, respectively. Set includes the patient's beliefs, attitudes, expectations, mood, personality traits, and psychological state (e.g., arousal, mindset) at the time of the session [22,49]. Physical surroundings (e.g., tent, nature, a hospital), support from therapists, and sensory stimuli such as music or lighting are part of what is understood as the setting [49,60]. Both set and setting have been found to be linked to therapeutic outcome as well as to how the psychedelic state is manifested in the subjective experience, in particular regarding the occurrence of mystical experiences [61]. For instance, prior to sessions, patients should ideally be in a calm, accepting, and open mindset, without having specific goals or rigid expectations [60]. Good settings are comfortable environments in which patients can relax, feel safe, supported and undisturbed. Nature has also been found to provide a beneficial setting for psychedelic experiences [49].

In psychedelic-assisted therapy, supervised sessions take place often in aptly decorated rooms with for example a comfortable sofa to lie on, and are accompanied by evocative music that may create a soothing auditory environment conducive to introspection and emotional processing [1]. Music has been found to enhance the overall therapeutic experience by evoking feelings of wonder, transcendence, and mysticality [49,62]. It's been suggested that set and setting manifest the experiential outcomes (e.g., occurrence of a mystical experience) in a session much more than purely the ingestion of a substance does, which then rather serves as a catalyst of such experiences [49,63]. This is historically mirrored in indigenous peoples' use of psychedelic substances in structured ceremonial rituals that have long acknowledged the importance of context and preparation [49,64,65].

2.3.2. Preparation and Integration

Both preparation and integration are recognized as relevant factors influencing therapeutic outcomes [1]. Preparatory sessions are held prior to drug administration sessions with the same therapists to create rapport and learn about the patient's life, personal struggles, traumas, relationships, and worldview. In subsequent drug-free integration sessions, patients are given the opportunity to reflect on, process and integrate their psychedelic experiences with the help of the therapists. The goal is to make sense of the potentially very profound insights and emotions that emerged during the acute drug experience and translate them into the context of daily life behaviour, personal values and goals, beliefs, and habits. Proper integration is thus crucially important to maximise the therapeutic benefit that can be derived from the experience because accommodation of the insights gained during the altered state into one's everyday life and value systems is necessary for lasting behavioural and psychological changes to occur [1,66].

2.3.3. The Therapeutic Relationship

Psychotherapy research has long recognized the therapeutic alliance—defined as the quality of the bond and collaborative relationship between therapist and client—as a crucial contextual/non-specific mechanism for positive treatment outcomes [1,67]. The therapeutic alliance has been found to be similarly significant in forms of pharmacotherapy, e.g., findings indicating that treatment response to SSRIs in depression is greatly influenced by the quality of the therapeutic relationship in accompanying psychotherapy [68,69]. In psychedelic therapy, the therapeutic alliance assumes even greater importance due to the profound, intimate, and intense experiences often elicited during high-dose drug sessions.

3. Indigenous Ceremonial Use: Ayahuasca, Mescaline, and Ibogaine

The use of traditional psychedelic plant medicines such as ayahuasca, mescaline, and ibogaine, has had a rich history rooted in indigenous spiritual practices long before the substances were

 doi:10.20944/preprints202407.2400.v1

researched in "western" clinical settings. Ayahuasca is a traditional Amazonian brew made from the Banisteriopsis caapi vine and the Psychotria viridis leaf, which contain β-carboline alkaloids acting as MAO-inhibitors and DMT, respectively. Ayahuasca is used in shamanic and spiritual rituals of indigenous tribes and communities and is known for its intense introspective visionary experiences and reported therapeutic benefits [17,70–72]. Among outcomes observed after consumption of ayahuasca are lower hopelessness and improvement of depression [17,72–74], as well as beneficial personality changes [75].

Mescaline is a naturally occurring psychedelic alkaloid found in several cactus species, most notably Peyote and San Pedro cacti. It produces visual hallucinations and altered states of consciousness similar to those of LSD and psilocybin, and has been used ceremonially in indigenous contexts in Central America for millennia [76]. Both mescaline and ayahuasca are technically also serotonergic psychedelics and have similar pharmacological and neurobiological mechanisms as the ones described above for psilocybin, LSD, and DMT.

Ibogaine is an alkaloid derived from the root bark of the African plant *Tabernanthe iboga* and is used in traditional African spiritual ceremonies. Ibogaine acts on various neurotransmitter systems, likely including serotonin, dopamine, opioid, sigma, and NMDA receptors, but its precise mechanism of action is not fully understood [77,78]. Ibogaine has been clinically researched mainly in the context of substance use disorder treatment, and anecdotal findings suggest that Ibogaine may help individuals struggling with various substance addictions [79], e.g., by reducing craving (through dopamine transporter inhibition and NMDA antagonism) and withdrawal symptoms (via opioid receptors) [77]. However, Ibogaine poses considerable risks because of its toxicity and potential adverse physical reactions, particularly its potential to cause cardiac arrhythmias, which arguably limits its therapeutic applicability [77–79]. The subjective experience is characterized by potentially uncomfortable re-experience of repressed memories and imaginary scenes with personal significance, accompanied by intense emotional release over a wide spectrum of emotions, and insight [78].

3.1. Arising Issues with Indigenous Plant Medicines

For many indigenous peoples of the Amazon, ayahuasca is integral to ritual practices, myths, cosmologies, art, music, and various aspects of cultural life [80]. Incorporating substances such as ayahuasca, mescaline or ibogaine into modern therapeutic practices necessitates a careful consideration of their traditional and shamanic contexts, as it raises issues of cultural appropriation [80,81]. For example, ayahuasca is now used in various countries outside the Amazon, including parts of South America, North America, Europe, Australia, New Zealand, and some parts of Asia. The consumption in possibly different cultural and geographical contexts and thus "settings", as well as different "sets" in terms of a consumer's cultural pre-convictions, affect how the altered state manifests phenomenologically, and also the meaning individuals derive from the experience [81,82].

4. Pharmacology and the Subjective 'Psychedelic' Experience

There is, notably, an ongoing debate regarding the necessity of the subjective experience for long-lasting clinical outcomes in particular for therapy assisted by psychedelic substances [5,83,84]. Some argue that acute subjective experience of a psychedelic state may not be essential for therapeutic outcomes, positing that an increase in neural plasticity, independent of subjective phenomena, is the primary, or at least a sufficient, mechanism driving therapeutic outcomes [83]. This perspective is analogous with the *psychoplastogen* model of psychedelics, and with what is called the "Molecular Neuroplasticity Theory of Psychedelic Therapy" [85].

These models suggest that isolating the non-hallucinogenic properties of psychedelics or other substances could provide effective therapeutic interventions, for example through concurrent administration of ketanserin to serotonergic psychedelics, which is a 5-HT2A receptor antagonist that subdues the changes in perception generated by the hallucinogen alone [34]. Indeed, compounds (such as *tabernanthalog*, a non-hallucinogenic analogue of DMT) have been engineered that promote cortical neuron structural plasticity without inducing an acute altered state, and that have

 doi:10.20944/preprints202407.2400.v1

demonstrated preclinical anti-addictive and antidepressant effects similar to those of ketamine in rodents [79]. Based on these findings, it has been suggested that the subjective alterations in consciousness may not always be strictly necessary for producing at least some therapeutic responses [83].

On the other hand, one of the most consistent findings in research about psychedelics is their ability to elicit experiences that are considered extraordinarily meaningful and transformative by the person going through them [39,51,86–88]. These profound psychological experiences have been found to be significantly associated with positive treatment outcomes in various contexts and across various substances [25,32,46,86]. The *quality* of the acute experience, and particularly the occurrence and intensity of a mystical experience, is the strongest predictor of the efficacy of psychedelic therapy for long-term mental health improvements [1,11,24,25,49,78,84,89]. These findings are more consistent with the *behavioural catalyst model* of psychedelics, which acknowledges a synergy between subjective experience and neurobiological mechanisms. It posits that the enduring therapeutic effects of psychedelics are mediated by the facilitation of transformative or disruptive subjective experiences during psychotherapy sessions and are implemented and reinforced neurobiologically during a window of increased plasticity [2,53].

Importantly though, it is arguable that not only serotonergic *substances* can evoke psychedelic states, but also other substances (e.g., ketamine) and even methods. Non-pharmacologically induced ASCs, for example through breathwork, some kinds of meditation, and sensory deprivation (presented in the following section), as well as near-death experiences and ancient dance and drumming rituals, share common aspects of phenomenology and neural correlates with those observed in drug-induced psychedelic states [90–94]. On the other end of the spectrum of theories, this may correspond to the one that Letheby [85] calls the "Implementational Neuroplasticity Theory": The psychedelic experience itself could trigger neuroplastic changes, regardless of whether it was induced by a substance or not. Molecular events like increased BDNF synthesis, in this view, are really a result, and not a cause, of the nature of the subjective experience.

Consequently, we would like to interpret the term 'psychedelic' to not include only drugs acting on a particular neurotransmitter receptor, but rather intentionally shift the focus away from psychedelic *substances* back to psychedelic *experiences*. The term "psychedelic" has been spuriously associated with experiences induced by substances that act as serotonin 5-HT2A receptor agonists, yet this definition, in our view, places undue emphasis on specific substances and their pharmacological actions rather than the *experiential phenomena* that the term was originally meant to describe, such as an expanded or dissolved sense of self, heightened emotions, altered perception and cognition, and visual mental imagery [41,95]. "Psychedelic" is simply a neologism derived from the ancient Greek words *psychē* and *dēlos*, intended to convey the concept of "mind-manifesting". Over time, the original meaning of "psychedelic" has been obscured by cultural shifts, i.e., the counterculture movement of the 1960s, the war on drugs, and a prevailing scientific reductionism that focuses on the physical/materialistic rather than the experiential [94]. Especially when talking about *psycho*therapy (as opposed to mere pharmacotherapy), however, the experiential aspect becomes increasingly relevant, as the subjective experience of the individual is essential for the therapeutic process. By broadening our understanding of "psychedelic" to encompass any experience that manifests the mind in an ultimately transformative way, we can more fully appreciate and understand the therapeutic potential of these experiences.

5. Non-Pharmacological 'Psychedelic' States

5.1. Breathwork

Nowadays, modern schools of breathwork, such as for example *Holotropic Breathwork* (which was developed by Stanislav and Cristina Grof as a substitute method to bring about cathartic psychedelic states of consciousness after LSD was effectively banned from psychiatric research and practice), *Rebirthing Breathwork* or *Sudarshan Kriya*® breathing, aim to induce altered states of consciousness to facilitate therapeutic change through active modulation of breathing rhythms [91]. Similar much older breathing practices such as yogic pranayama have been utilized for millennia in

 doi:10.20944/preprints202407.2400.v1

spiritual and healing practices [96]. Breathwork sessions are often guided by trained facilitators and frequently accompanied by evocative music, although the specific context can vary depending on the philosophy of each breathwork school [91]. The common technique of these modern forms of breathwork is *conscious connected breathwork* (CCB), which induces respiratory alkalosis by increasing CO2 elimination, leading to cerebral vasoconstriction and reduced oxygen delivery to the brain [91,97]. Alkalosis disrupts GABAergic inhibition, increasing neuronal hyperexcitability and neurometabolic demands that are not met by the reduced oxygen supply [98,99]. The hypoxic state eventually results in heightened arousal, increased alertness, and stimulation of the sympathetic nervous system, consequently contributing to intense emotional and somatic experiences that are integral to the therapeutic processes taking place during the breathing session [91].

Participants report acute changes in the intensity and content of thoughts and emotions, sense of self, as well as perceptual distortions, subjective visions, and somatic sensations such as for example tingling, roaring in the ears, light-headedness, or sweating [100]. In a bulletin for the Multidisciplinary Association for Psychedelic Studies (MAPS), 80% of psychiatric inpatients described their Holotropic Breathwork experiences as 'psychedelic' [90], and in a day-long workshop approximately 10% of participants met the criteria for a "complete" mystical experience [101], which is comparable to the 11% rate observed in participants administered a 10 mg/70 kg dose of psilocybin [87]. Similar to substance-induced psychedelic therapy, breathwork sessions aim to achieve emotional breakthroughs or catharsis and gaining insights via the re-experiencing of significant autobiographical events and through mystical-type experiences including ego dissolution or oceanic boundlessness [101–103].

Despite being in early stages of scientific research concerning experiential states and outcomes, breathwork represents a promising non-pharmacological alternative for inducing psychedelic-like alterations in consciousness that may offer therapeutic benefits [91]. Indeed, in a recent study in this special issue, Breathwork was used as a control group to assess changes in well-being, resilience, self-compassion, and personality after an Ayahuasca experience. In follow-up, *both* groups showed comparable changes and improvements in all measurements that did not differ significantly from each other [104].

5.2. Meditation

Recent research indeed also suggests that there might be significant phenomenological and neurophysiological overlaps between meditation-induced trance states and those induced by psychedelic substances [105–107]. One example are their effects on brain regions involved in self-referential awareness [108–110]. Both psychedelic and very deep meditative states of advanced practice can be characterized by an experiential quality of oneness and an altered sense of self, such as that of complete dissolution of ego boundaries, both of which have been proposed as a key processes underlying therapeutic benefits [107,111,112] and will be elaborated on later in this review. Indeed, it has been noted that most meditation practices, regardless of tradition or technique, have it as their ultimate aim to transcend ego self-identification and achieve this unified state of "nondual" awareness that is so characteristic of psychedelic-occasioned mystical experiences [113,114].

5.3. Sensory Deprivation

As a third example, sensory deprivation can induce altered states of consciousness that closely resemble those induced by psychedelic substances. Sensory deprivation involves the intentional reduction or elimination of sensory input, which can be achieved using methods such as darkened chambers, soundproof spaces, or floatation tanks [115]. Floating induces a variety of neurophenomenological effects similar to those caused by psychedelics, such as ego dissolution, disembodiment, transcendence of space and time, and hallucinations [116,117]. Sensory deprivation can also trigger visual and auditory hallucinations, as the brain generates its own sensory signals in the absence of external stimuli [116,118,119]. These hallucinatory experiences and the resultant cognitive flexibility may lead to novel insights and challenge existing cognitive structures, similar to the effects of psychedelic substances [119–121]. Additionally, the disruption of default mode network

 doi:10.20944/preprints202407.2400.v1

activity observed during floatation is comparable to the effects seen with psychedelics, suggesting that both modalities can lead to ego dissolution and a heightened state of entropy in cognitive processing [105,109,122].

6. Subjective Psychological Experiences and Processes Triggered by the Psychedelic State

6.1. Transcendent and Mystical Experiences

In the study of therapeutic change, the term "transcendence" is used to describe moving beyond perceived limitations and problems caused by dysfunctional beliefs or entrenched thought and behaviour patterns [28]. This process of "stepping outside" of the context where these limitations exist, crucially, always requires individuals to alter or redefine their sense of self. This aligns with self-transcendent experiences during psychedelic states – such as mystical states that by definition involve profound shifts in the perception of self [112].

Psychedelic experiences have consistently demonstrated the capacity to include so-called mystical states [32,49,123] that are experienced as deeply meaningful and transformative by the individuals undergoing them [86]. "Mystical experiences", per definition, are profound states characterized by an experience of unity, interconnectedness, and transcendence beyond the conventional sense of self and time. They are marked by intense positive emotions like joy and bliss, deep peace, a sense of safety, and love; as well as the sense of having encountered some kind of ultimate reality and insight [22,49,123]. They are associated with long-term positive change [1,25,42,124,125] such as for example in personality traits, well-being and life satisfaction, greater sense of meaning and appreciation for life, self-acceptance, and creativity, as well as decreased existential anxiety in the terminal ill [1,45,49,126,127].

The most widely used tool to quantify mystical experiences is the Mystical Experience Questionnaire (MEQ), a scale that is based on an identification of common core characteristics of mystical experiences by Stace [128] that he argued to be universal; i.e., independent of culture and not tied to any specific religion or philosophical system: experience unity and ego dissolution, noetic quality, a sense of sacredness, positive mood, transcendence of space and time, paradoxicality, and ineffability [129]. The most recent version of the questionnaire, the MEQ-30 [130], assesses the subjective phenomenology of mystical experiences across four subdimensions: mysticality (which includes the first three of Stace's core characteristics), positive mood, transcendence of space and time, and ineffability. For example, MDMA increases feelings of unity and positive mood that act therapeutically but might not induce "complete" mystical experiences as frequently as psilocybin [32,131].

Rather than being a mechanism as such, the quality and intensity of mystical experiences have been shown to significantly mediate therapeutic outcomes [11,14,29,123] via experiences of unity, ego dissolution, awe, insight, emotional breakthrough, and acceptance, as well as changes in beliefs about the world and the self.

6.2. Unity and Ego Dissolution

One key feature of mystical experiences is a profound sense of connection with the universe or self, referred to as "unity" [125]. This "extrovertive" unitive aspect is represented by high scores in the "mysticality" factor of the MEQ as well as the "oceanic boundlessness" dimension of the Altered States of Consciousness (ASC) scale, and it has been shown to predict long-term therapeutic outcomes [18,25,49], for example for alleviating depression and reducing death anxiety in both terminally ill patients and healthy participants [22,23,89]. During these experiences, individuals often report feelings of empathy, (self-)compassion, and profound interconnectedness. Neuroimaging studies have suggested that these unitive feelings are associated with increased global functional connectivity in the brain, reflecting a more integrated mode of brain function during psychedelic states [109,132].

The second, "introvertive" aspect of unitive experiences, known as "ego dissolution" or "ego death," involves a temporary loss of the sense of self and is considered a core therapeutic mechanism

 doi:10.20944/preprints202407.2400.v1

of psychedelics [85,106]. Ego dissolution is characterized by "complete absence of self-reflective thought, the experience of an 'I' as being distinct from the world, and of the sense of having a bodily self or a narrative/reflective self" [22], which can be both pleasurable and initially frightening. These "ego death" experiences can sometimes be preceded by extreme tension and distress, such as feeling like or visions of dying, but ultimately lead to significant therapeutic benefits nonetheless [133–135]. Research indicates that individuals who undergo "complete" ego dissolution are more likely to report positive clinical outcomes and long-term changes in worldview and personality traits, particularly openness [25,41,44,50,105].

It's been proposed that instances of ego dissolution, e.g., as occasioned by ketamine or DMT, share certain similarities with near death experiences (NDEs) [136], which are equally renowned for changing a person's worldview and spiritual beliefs [14,137]. NDE's are deeply transformative experiences that may facilitate insights which help to make sense of death, instigate increased meaning in life, and change embraced values [14], thereby making death seem less threatening [45]. The long-term self-transformational effects of NDE's seem to be comparable with those of psychedelics and present opportunities for foundational changes in self-identity, personality, values, and purpose [138].

6.3. Awe

Findings support that awe is a core characteristic of mystical experiences and thus a factor for long-term therapeutic outcomes [123], making it a significant process in the subjective psychedelic state (MacLean et al., 2012). Awe is an emotion associated with profound pleasure, sometimes mixed with fear, that arises when individuals process stimuli or ideas that are perceived as vast and extending well beyond the sense of self [140]. In the context of psychedelic experiences, the profound sense of awe can prompt individuals to adapt their existing mental frameworks to accommodate these novel perspectives. Mirroring aspects of ego dissolution, experiences of awe often reduce self-referential processing [141], fostering a sense of connection to a larger collective such as one's community or species [132,142–144]. The intense and awe-inducing nature of psychedelic experiences is hypothesised to facilitate overcoming personal obstacles by prompting a revision of existing mental schemes, also known as accommodation [139]. Encountering something awe-inspiring which transcends current frames of reference can have beneficial effects on well-being and is associated with increased life satisfaction [145,146], more positive emotions [147], and greater meaning in life [148].

6.4. Long-Term Changes in Beliefs – Cosmology, Meaning, and Self

Ultimately, all the psychological processes inherent to mystical experiences may lead to fundamental changes in a person's belief and value systems. Being inherently spiritual on account of their transcendent nature, hallucinogenic and particularly mystical experiences have been found to profoundly shift individuals' beliefs about the world and about themselves, and even occasion so-termed "ontological shock", a dramatic revision of prior beliefs [22,49,149]. Indeed, a recent study revealed that a DMT experience can significantly impact individuals' worldviews, with over half of the participants no longer identifying as atheists after their experience with DMT as opposed to before [150]. Additionally, another recent study found that participants in a psychedelic retreat experienced shifts in their metaphysical beliefs, transitioning from physicalist or materialist perspectives to more panpsychist ones [151].

It's important to note that even though spirituality or religiousness are by no means prerequisites for either mystical experiences to occur or for them to have therapeutic value, but that these mystical experiences, on account of their transcendent nature, are fundamentally spiritual. While purely secular interpretations of psychedelic experiences can certainly provide valuable insights and improvements in psychological processes and well-being, they may limit the full potential to be derived from these experiences. It seems thus advisable to achieve a balance between acknowledging the diverse spiritual experiences and their metaphysical implications that may arise during e.g., drug administration sessions and respecting the individual's autonomy to interpret these experiences and assign meaning to them within their own belief system [49]. This seems even more

 doi:10.20944/preprints202407.2400.v1

relevant when considering that psychedelic substances have been found to increase suggestibility [38,152], i.e., a heightened responsiveness of individuals to suggestions, guidance, or external stimuli during and after a psychedelic experience.

This effect is possibly evoked or strengthened by relaxed prior beliefs and convictions. Integrating the entropic brain theory and free energy principle framework, the REBUS model (reviewed elsewhere in more detail) attempts to explain how psychedelic-induced neural entropy could temporarily induce a relaxation of precision weighting [152]. This leads to a state in which established beliefs and reinforced patterns of attention are essentially more 'plastic', in a higher-level sense concerning models of identity, ego, and sense of self [153], which makes experiences such as ego dissolution possible. In states of increased neural entropy and uncertainty, the extra-ordinary may be no longer "explained away" by the brain's prior convictions and thus make it into conscious reflection. Additionally, this state provides a chance to revise previously entrenched cognitive patterns and self-models that may contribute to psychiatric complaints, as they are temporarily made more amenable to alternative viewpoints and thus constructive change [2,152,154,155].

The so-called Metaphysical Belief Theory (MBT) of psychedelic therapy proposes that its therapeutic efficacy stems indeed from inducing enduring non-naturalistic beliefs centred around a "Joyous Cosmology" that is encountered during the mystical experience [85]. 'Joyous Cosmology is a term coined by Alan Watts [156] to describe the largely ineffable transcendent vision of non-naturalistic metaphysical ideations. According to MBT, psychedelic states facilitate lasting benefits by first triggering mystical experiences characterized by such a cosmology, which subsequently foster strong beliefs in it. Thus, these belief changes, rather than the mystical experience itself, are seen as primarily responsible for therapeutic outcomes [85]. This theory is not uncontroversial: the main objecting concern is that these practices may promote or rely on beliefs that, while comforting or psychologically beneficial for the individual, are not necessarily true or grounded in reality. This may raise ethical questions about whether it is appropriate to essentially encourage beliefs in mental health treatment that are not based on evidence, despite their pragmatic value for therapeutic outcomes [82]. On the other hand, if the beliefs induced by psychedelic experiences lead to genuine improvements in mental health and well-being, then the role they have in therapeutic practice might arguably be justified. It may be argued that determining the "truth" or "falsehood" of beliefs based on objective reality is beyond our capacity anyways, given our current understanding of the nature of consciousness and the fundamental principles of the universe.

It has also been suggested that the therapeutic effects of psychedelics that correlate so significantly with the occurrence of mystical experiences do not necessarily depend on the conscious endorsement of changed metaphysical beliefs, but rather that they arise from non-reflective mental representations of the encountered vision [85]. The idea would be that psychedelic therapy operates akin to a kind of 'inverse PTSD' scenario [157], where a singular peak experience and the memory of it yield enduring positive effects on well-being by functioning as an embodied beacon of hope.

Nevertheless, even when disregarding changes in metaphysical beliefs as the driving therapeutic force, deeply meaningful experiences of self-transcendence do appear to frequently prompt re-evaluations of personal narratives, life perspectives, and core beliefs. This brings about positive therapeutic change by helping individuals make sense of their own identity and place in the world, thereby alleviating symptoms of e.g., depression [22,126,158]. They may fundamentally challenge the conventional or, in relation to psychopathology, dysfunctional ways of perceiving meaning as well as one's relation to the world, and thus offer individuals new ways to evaluate and process their struggles and potentially adverse autobiographies. Like in 'regular' cognitive-behavioural therapy, one proposed mechanism of change in psychedelic-assisted therapy is indeed the breaking of previously rigid maladaptive emotional and cognitive patterns, and "restructuring" them in a more adaptive and functional way for the patient [3,55].

Psychedelic states, then, might operate therapeutically by challenging one's core assumptions about oneself, ine's life, and one's relationship with the world. The critical factor might not necessarily involve a fundamental change towards non-naturalistic metaphysical beliefs, but rather the disruption and re-evaluation of mental representations of the self, and the self in relation to the

 doi:10.20944/preprints202407.2400.v1

world [85]. Ego dissolution, a phenomenological manifestation of self-disruption through relaxed priors, might be seen as a more naturalistic hallmark of what we call mystical experiences. Positive treatment outcomes associated with, for instance, psilocybin- and ketamine-assisted therapy have indeed been attributed to enduring alterations in views on the self [3,14,153,159]. This relationship is in alignment with neuroscientific findings describing psychedelic states that suggest alterations in the default mode network and salience network, both of which plausibly influence changes in self-perception [109,160]. In a way, the experiential insight into alternative ways of perceiving the self brings the earlier discussed original notion of 'psychedelic' back full circle: revealing one's mind, and its potential, to oneself.

6.5. Emotional Breakthrough

The occurrence of so-called "emotional breakthroughs" during psychedelic experiences has been found to strongly predict improvements in psychological well-being and is generally correlated with beneficial clinical outcomes [22,161–163]. These breakthroughs, whose conceptualisation is similar to the psychoanalytic notion of catharsis [163,164], are facilitated by intensification of and increased access to (conscious or unconscious) emotions and cognitions, which may be enabled by the effects of a (psychedelic) drug or other mind-manifesting methods such as breathwork or floatation-REST [41,116,165,166]. In a supportive therapeutic setting, this increased access and amplification of emotions can facilitate emotional breakthroughs, leading to feelings of resolution, relief, and insight [163]. The Emotional Breakthrough Inventory (EBI) was recently validated as a tool to measure these aspects of psychedelic experiences and has been shown to predicts changes in well-being after psychedelic use [163].

6.6. Insight

"Insight" can be brought on by experiences of unity, ego dissolution, emotional breakthroughs, reliving of autobiographical memories, or perspective shifts, but also occur independently. Insight is generally considered a highly essential mechanism of core change in almost any psychotherapy [3,28,167]. In the context of therapeutic psychedelic experiences, insight encompasses a profound realization that may involve gaining a deeper understanding of one's own (possibly dysfunctional) thoughts, emotions, behaviours, personal histories or current life circumstances [168], like for example the root causes or maintaining factors of a patient's issues or disorders [3,169]. Additionally, insights may extend beyond the personal realm to encompass deep metaphysical understandings of fundamental truths about the nature of reality and the constructed sense of self [26].

In the context of psychedelic experiences, insight has been characterized by its intuitive (rather than intellectual/rational) nature, with individuals experiencing sudden breakthroughs in understanding accompanied by feelings of certainty and positive affect [170]. This understanding aligns with Stace's notion of "the noetic quality" (from the Greek word "*noesis*", which means "inner wisdom" or "intuitive understanding") [171]. These insights are frequently cited as fundamentally important to enduring positive outcomes in therapy, mediating improvements in e.g., well-being, psychological flexibility, depression, anxiety, and substance use [84]. Insight in psychedelic-assisted therapy is equated with a restructuring of existing patterns of cognitive schemas and beliefs into novel understandings of past experiences or the self [26], for example renewed beliefs in one's own self-efficacy and worth, or one's ability to stay abstinent, and a stronger sense of connection with oneself and the world [36,84,172,173].

The Psychological Insights Questionnaire (PIQ) was developed to measure participants' experiences of sudden understanding into their memories, emotions, relationships, behaviours, or beliefs that may occur subsequent to the ingestion of psychedelics [174,175]. It has been observed that insight effects predicted self-reported reductions in depression and anxiety, as well as changes in well-being even when controlling for the occurrence of mystical experiences [47,63,84,176].

 doi:10.20944/preprints202407.2400.v1

6.7. Perspective Shift

Psychopathology is, among other things, characterized by patients' restricted ego-centric perspective which is exemplified in the act of ruminating or common feelings of despair and hopelessness in depression. A perspective change as enabled by consciousness-altering substances or methods provides the patient not only with a temporarily altered view on their own "self", but also a new and different space to look for solutions and more functional ways of dealing with their problems [3,21,22,86]. As mentioned previously, an embodied emotional recollection of a psychedelic experience may stimulate people to "un-self", i.e., to transcend biased or limiting perceptions of their self in their daily life which may fuel gradual change and healing [177].

Notable with regards to mystical experiences is that particularly the shift to the experience of unity/interconnectedness with the world and with others and away from ego-centric identification have been hypothesized to account for the therapeutic effects of psychedelics across various disorders [3,14]. Another example is ketamine, for which reduced self-referential awareness in the dissociative experience is stressed as a factor enabling severely depressed patients to engage in therapy more meaningfully as they are afforded a "break" from their ordinary ruminating mind, suicidal thoughts, negativity, and hopelessness [14,21] . As Hanna et al. [28] suggest, gaining an overarching perspective by simply stepping back and detaching from the context of a problem can itself facilitate more effective coping.

Furthermore, the widening of a self-centred point of view is often paralleled by a sense of connectedness and peace, and associated with increased empathy and better relationships [178]. The shift in perspective fosters greater connectedness not only with oneself, but also a different way of relating to people, the external world, and life [49,125,135,137,173], counteracting feelings of disconnection and isolation commonly associated with depression (Breeksema et al., 2023).

6.8. Acceptance

The shift from avoidance to a state of acceptance, openness, and surrender is a process that is seen as central in psychedelic treatments [179] and also for example in meditative practice [168,179–182]. It has been linked to the occurrence of mystical experiences under psilocybin [159] and is also a key aspect of mindfulness [49]. More generally, by adopting an accepting and compassionate perspective towards the world and oneself, people might be better equipped to handle life's challenges without resorting to avoidance behaviours [183].

Patients undergoing psychedelic therapy for a variety of conditions have identified broadened emotional spectrum and heightened emotional experiences as characteristic of the psychedelic state and also found them therapeutically significant [86][36,135,184,185]. These intense emotional experiences might initially involve confrontation with difficult or painful emotions, however the acceptance of them can ultimately lead to a feelings of catharsis and release, even joy, bliss, or profound forgiveness and love [85].

In addition, Thal et al. [3] highlight that substance-induced dissociation from conditioned roles and habits may foster acceptance of *oneself*, which has also been reported by participants of e.g., ayahuasca [186] or breathwork [104] sessions. Acceptance can also target aspects of one's life, such as terminal illness [187] or aspects of one's biography that were previously avoided [85]. Shifts from experiential avoidance to acceptance may again be facilitated by the relaxation of higher-level beliefs that would result in avoidance of e.g., certain emotions or memories [3], as described above for metaphysical and self-related beliefs.

Moreover, avoidance sensitivity, meaning the tendency to avoid aversive aspects of psychedelic experiences, can exacerbate potential adverse responses in the acute psychedelic state, while embracing these experiences can lead to more positive outcomes: Participants have reported that reducing resistance and embracing the experience during sessions with substances like esketamine led to calmer, smoother, and more pleasant experiences, contributing to a positive affect post-session. "Letting go" was not only necessary for the experience to unfold positively but was considered to be a very meaningful and even key therapeutic aspect of their experience [60].

 doi:10.20944/preprints202407.2400.v1

6.9. Re-Experiencing and Reconsolidation of Memories

Re-experiencing and reconsolidation of memories are hypothesised to play a crucial role in the therapeutic efficacy of psychedelic-assisted therapy [2,3,188]. Psychedelic-induced states, as well as experiences during breathwork and meditation, often involve emotional recollections and reflections on significant life events and relationships, ranging from past transgressions and unresolved traumas [189] to memories providing insights into one's own ways of being and behaviour [1]. This process thus often also involves mindfulness, where patients first become aware of unconscious thoughts and emotions and are furthermore enabled to evaluate them open-mindedly. Due to their empathogenic effects, substances such as for example MDMA allow patients to revisit and re-process traumatic memories without experiencing overwhelming emotional discomfort, judgement, or re-traumatisation [3,190], facilitating increased feelings of acceptance and resolution. For instance, a key symptom of PTSD is the occurrence of involuntary memory intrusions associated with the traumatic event. Through the process of memory reconsolidation, previously frightening stimuli lose their threat association and become reintegrated in a less problematic way [3]. This process is akin to exposure therapy for PTSD, where therapeutic change is a result of new emotional responses to initially very distressing memories becoming integrated [191]. The metaphor of the "helioscope" has been proposed to explain how psychedelics may help a patient choose and process traumatic memories without being severely overwhelmed by their emotional charge [192].

It might be worth noting that the positive effects of these recollections are not necessarily dependent on the factual accuracy of the memories themselves but rather on the release and re-assessment of trauma-related emotions [190]. Additionally, the potentially ineffable nature of these memories in the context of a mystical experience does not seem to diminish their therapeutic impact or perceived meaningfulness [184].

6.10. Challenging Experiences

It is worth discussing that certain experiences occurring within psychedelic states may be challenging and acutely unpleasant to the individual, such as ego dissolution or the re-experience of traumatic memories. For instance, in one survey, about one-third of participants rated their mystical experience among the top five most psychologically challenging experiences they had ever faced [193]. The frequently used and validated Challenging Experience Questionnaire (CEQ) is a self-report tool designed to measure the intensity and nature of challenging experiences encountered during psychedelic sessions. It encompasses seven key domains: fear, grief, physical distress, insanity, isolation/alienation, death, and paranoia [194]. The CEQ is particularly sensitive to difficult psychedelic experiences, and it has been found to indicate that the intensity of such experiences is indeed predictive of positive long-term outcomes (e.g., higher scores tended to be accompanied by higher degrees of mystical experience and psychological insight), while prolonged struggle may predict negative outcomes [25,194,195]. The subscales of the "Dread of Ego Dissolution" dimension within the 11D-ASC questionnaire measure these negative aspects of altered states, namely anxiety and impaired cognition and control [196].

In lay circles, instances of adverse experiences are frequently termed "bad trips"; it should however be kept in mind that challenging experiences are usually transient and can be inherently and exceedingly valuable to therapeutic progress. Intense emotions such as anxiety, confusion, grief, anger, or distress can be unpleasant aspects of psychedelic experiences. However, it is not surprising that a profound restructuring of the self, way of being, or way of perceiving and coping with the world or life events (resembling perhaps the ultimate goals of psychedelic therapy) can involve intense turmoil, stress, and internal conflicts before the significant change occurs (Hanna, 1995).

Such episodes of difficult self-experiences, whilst initially upsetting, are sometimes seen as essential for emotional breakthroughs and insights [134], and do align with, for example, psychoanalytic theories that emphasize the need to overcome psychological resistance for therapeutic progress [164] and the humanistic notion that coming face to face with a problem is necessary to transcend it [28]. Similarly, in modern exposure therapy, which shares parallels with confrontational aspects of psychedelic experiences in its working mechanisms, braving discomfort plays a crucial role

 doi:10.20944/preprints202407.2400.v1

in emotional processing and subsequent symptom reduction [197]. Accordingly, challenging experiences in psychedelic therapy can enable individuals to confront, process, and integrate significant (and sometimes unconscious) memories and emotions, ultimately generating new helpful perspectives, coping mechanisms, and self-awareness [1]. The deliberate/intentional and controlled induction of discomfort or stress, as it happens also for example in breathwork sessions, can reduce long-term anxiety through gradual adaptation [198,199].

Crucially, therapeutic support is vital in guiding individuals through these challenging moments, ensuring that transient distress leads to meaningful insights and lasting benefits and not further destabilisation [60], which is of importance especially in clinical populations. Proper preparation, monitoring, and ongoing support with integration are critical, as they help contextualize and ground these experiences, maximizing their therapeutic value [1,61,134,195].

Nonetheless, the unusually vulnerable state participants are placed in during psychedelic experiences can lead to challenging experiences that have serious long-lasting negative effects, such as for example prolonged existential struggle, social disconnection, depersonalization and derealization, if not properly managed [200,201]. While cases in the literature might seem rare, there is a realistic possibility that they are overlooked or under-reported due to flawed designs, small sample sizes, imprecise follow-ups, or biased reporting [202]. Additionally, it is well possible that not all contraindications are fully understood at this time, increasing the risk of adverse reactions and experiences. Therefore, it is essential to take comprehensive precautions to ensure patient safety. This highlights the importance of a nuanced view on challenging experiences, and on ongoing harm reduction research to identify and mitigate risks associated with psychedelic treatments.

7. Discussion

The findings presented in this review speak to the relevance of the subjective experience to therapeutic outcomes, rather than being a mere a 'side effect' of the *non*-experiential, low-level molecular mechanisms that promote neural plasticity. While the occurrence of mystical experiences seems to be the strongest predictor of positive outcomes, the literature of the field yields numerous other psychological processes, such as insight, emotional breakthrough, acceptance, re-experiencing of memories, and certain aspects of challenging experiences, that are significantly associated with positive change.

We have additionally discussed in detail the changes in metaphysical as well as self-related beliefs and their respective contributions to observed outcomes. Briefly, mystical experiences facilitated by psychedelic substances as well as other mindful practices are thought to be able to profoundly shift belief systems and thereby provide therapeutic benefits. However, these benefits may not solely depend on changes in metaphysical beliefs but rather on the re-evaluation of self-perception and personal narratives as well. In essence, psychedelic experiences facilitate not only plasticity on a pharmacological/neuronal level, but also in cognitive patterns and patterns of meaning. Importantly, these kinds of plasticity do not necessitate a substance to 'reveal their mind' to a person, as they are not limited to *pharmacologically induced* altered states.

Earlier in this review, we discussed modern forms of breathwork [91,103,203], as well as meditation [204], and sensory deprivation [116,117] as non-pharmacological modalities to induce states that accurately might be described as 'psychedelic' in the original sense of its meaning. Although investigations into their therapeutic efficacy and distinct neurophysiological correlates are partly limited to date, existing findings offer sufficient insights to infer their change-driving mechanisms. Importantly, some of them overlap considerably with the subjective states of pharmacologically induced altered states that are more readily and commonly considered 'psychedelic'. For example, among proposed therapeutic mechanisms of breathwork are re-experiencing of significant memories, emotional breakthrough, insight, change of beliefs, and mystical experience [101–103,165,205]. Similarly, meditation has recently been investigated for its potential to induce mystical experiences [204,206–208]. This additionally supports the notion that therapeutic processes tied to subjective and 'psychedelic' experiences that exist across various modalities (and beyond substances) and are fundamental in facilitating positive therapeutic change.

 doi:10.20944/preprints202407.2400.v1

A purely neurochemical/pharmacological approach thus seems reductionist when asked to account for the therapeutic potential of these extra-ordinary states.

7.1. Implications for Research

Incidentally, the initial question of whether the acute subjective experience is essential for the therapeutic effects of psychedelic therapy at all effectively invites a discussion of much broader philosophical fundamental principles in psychology, specifically concerning our understanding of psychopathology and what constitutes psychotherapy. This discourse hints at a potential paradigm shift away from a traditional medical model towards a more humanistic and experience-focused approach to understanding mental pathology and treatment, which is very relevant to our understanding of how therapy in altered states of consciousness may work therapeutically. Historically, the medical model has dominated the field of mental health, viewing mental disorders primarily as biological diseases to be treated with medication or other medical interventions. This approach somewhat mirrors the psychoplastogen model of psychedelics, as it solely emphasizes the therapeutic neurobiological effects of these substances as a novel kind of pharmacotherapy. However, our psychological and psychopathological realities as sentient humans are shaped most of all by our subjective perspective and perception. In the field of medicine, a physician might identify a patient's condition based on symptoms and provides appropriate treatment aimed at curing the illness. Similarly, proponents of the medical model in psychotherapy assert that therapists diagnose patients using a similar symptom-based approach and consequently apply treatments aimed at alleviating their psychological distress. This perspective arguably overlooks the fundamental nature of psychotherapy as an inter- and intrapersonal process, distinct from medical practice and pure technical intervention [209]. The emphasis instead lies on improvement on account of the therapeutic relationship and psychological exploration that provides solutions and new perspectives, rather than being a mere medical-pharmacological intervention [67]. Psychological problems are situated in the context of life as it is experienced by a person, and most often in relation to others. From an existential-phenomenological perspective, disorders are not as much diseases as they are alterations of being-in-the-world that are experienced as distressing or impairing [209].

*Psycho*therapy should aim to acknowledge the complexity of human psychology and the interconnectedness of biological, psychological, and social factors in shaping mental well-being. Therefore, instead of trying to rigidly separate therapeutic efficacy of psychedelic therapy into subjective versus neurobiological components or argue away either of them, it seems much more reasonable to acknowledge their interdependence. There is no subjective experience without neurological underpinnings, and likewise neurophysiological changes typically have mental consequences. Taking a holistic view of individual patients as experiencing beings rather than objectified "broken machinery" necessitates integrating psychological mechanisms of change, and therefore subjective experiences, into our understanding of mental health treatment, and especially into psychedelic therapy. As long as we label clinical interventions involving the administration of psychedelic substances as "psychedelic-assisted psychotherapy" (and not just "substance-assisted therapy"), the importance of the subjective experience (that is, in addition, so clearly context-dependent) in the meaning-making therapeutic process seems undisputable.

On this note, the accuracy of the term "psychedelic-assisted psychotherapy" has also been called into question, since at least in case of therapy sessions involving the administration of high doses of psychedelics, the experience itself is, in fact, the main constituent of the therapy. Therapists supervise these drug sessions primarily for safety reasons rather than for therapeutic efficacy. For example, with high doses of psilocybin or LSD, there is typically no "psychotherapy" that might be assisted by the drug, because the acute psychedelic state makes interactions of conventional psychotherapy largely impossible [210]. In contrast, MDMA-assisted therapy, for example, involves a therapeutic relationship process that is augmented by a pharmacological agent that alters consciousness. The medication serves as a catalyst within the treatment process rather than constituting the treatment itself, making it, again, more than purely a medical-pharmacological treatment. We might therefore need to make a more explicit and nuanced difference between "psychedelic therapy" and

 doi:10.20944/preprints202407.2400.v1

"psychedelic-assisted therapy", depending on whether (a) the subjective transcendent experience of a drastically altered state constitutes the therapy (by changing self-views, world-views, meaning, increasing insight and acceptance etc.) or (b) a slightly altered state (such as with moderate doses of a drug, or specific breathing patterns) supports a more regular psychotherapeutic intervention. In *both* cases however, psychological mechanisms within the subjective experience of the patient play an undeniably essential role for therapeutic success [22,84].

Consequently, while pharmacological agents such as psychedelics surely provide a neurological foundation conducive to healing, the accompanying psychological processes remain crucial for achieving lasting therapeutic outcomes. For example, disorders rooted in irrational core beliefs, which are deeply embedded within the individual's cognitive framework, certainly require more than just pharmacological intervention for meaningful change. These beliefs, foundational to a person's worldview, are not easily altered by chemical agents alone and necessitate a comprehensive psychological integration process. It must be noted that this transformation can be lengthy, requiring shifts in viewpoints that eventually lead to changes in behaviour. We do no argue that psychological experiences during psychedelic therapy or experiences are always singular solutions, but rather that they can act as eye-openers that challenge limited beliefs and ordinary perspectives manifested by or in psychopathology. At the same time, while psychedelic states may be able to facilitate significant insights and breakthroughs, not all psychological/psychiatric disorders can be resolved solely through these means either. Neurochemical imbalances and aberrant neural circuitry are frequently implicated in various psychiatric conditions, and they do offer potential targets for pharmacological interventions.

In essence, the debate around subjective experience in substance-assisted (psycho)therapy highlights the necessity of a more nuanced, multi-level, interdisciplinary approach that *bridges* pharmacological and psychological interventions to truly understand how therapeutic change is sustainably achieved. As Garcia-Romeu and Richards [1] have stated: "we propose this paradigm serves as an invitation for psychiatry overall to return to a more holistic, humanistic-existential, or biopsychosocial framing of the person and his/her issues as a whole within a larger social matrix and fabric of meaning, as opposed to approaches that reduce the person to mere neurochemistry, symptoms, and disorders".

8. Conclusion

This narrative review has emphasized the positive changes facilitated through psychedelic altered states of consciousness rather than psychedelic substances alone. In addition to pharmacological approaches, exploring non-pharmacological methods to harness the potential of psychedelic-like effects for therapeutic and self-realization purposes seems worthwhile and could expand the available repertoire of interventions.

The findings, moreover, suggest that a purely medical and neurobiological perspective on psychological health is too limited and should not overshadow the significance of phenomenological experiences in understanding and treating psychological issues that manifest in subjective realities of human individuals. This is particularly relevant for therapies that utilize psychedelic states, as the psychological processes inherent to the subjective experience of those states show clear associations with subsequent positive change. An integrative model is needed to account for the interdependence of psychological and pharmacological dimensions that shape psychopathology and mental health treatment.

Author Contributions: Conceptualization, R.W.; writing—original draft preparation, R.W.; writing—review and editing, H.S.; supervision, H.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Garcia-Romeu, A.; Richards, W.A. Current Perspectives on Psychedelic Therapy: Use of Serotonergic Hallucinogens in Clinical Interventions. *Int. Rev. Psychiatry* **2018**, *30*, 291–316, doi:10.1080/09540261.2018.1486289.
2. Heifets, B.D.; Olson, D.E. Therapeutic Mechanisms of Psychedelics and Entactogens. *Neuropsychopharmacology* **2024**, *49*, 104–118, doi:10.1038/s41386-023-01666-5.
3. Thal, S.B.; Bright, S.J.; Sharbanee, J.M.; Wenge, T.; Skeffington, P.M. Current Perspective on the Therapeutic Preset for Substance-Assisted Psychotherapy. *Front. Psychol.* **2021**, *12*, doi:10.3389/fpsyg.2021.617224.
4. Andersen, K.A.A.; Carhart-Harris, R.; Nutt, D.J.; Erritzoe, D. Therapeutic Effects of Classic Serotonergic Psychedelics: A Systematic Review of Modern-era Clinical Studies. *Acta Psychiatr. Scand.* **2021**, *143*, 101–118, doi:10.1111/acps.13249.
5. Cameron, L.P.; Patel, S.D.; Vargas, M.V.; Barragan, E.V.; Saeger, H.N.; Warren, H.T.; Chow, W.L.; Gray, J.A.; Olson, D.E. 5-HT2ARs Mediate Therapeutic Behavioral Effects of Psychedelic Tryptamines. *ACS Chem. Neurosci.* **2023**, *14*, 351–358, doi:10.1021/acschemneuro.2c00718.
6. Carhart-Harris, R.; Giribaldi, B.; Watts, R.; Baker-Jones, M.; Murphy-Beiner, A.; Murphy, R.; Martell, J.; Blemings, A.; Erritzoe, D.; Nutt, D.J. Trial of Psilocybin versus Escitalopram for Depression. *N. Engl. J. Med.* **2021**, *384*, 1402–1411, doi:10.1056/NEJMoa2032994.
7. Carhart-Harris, R.L.; Roseman, L.; Bolstridge, M.; Demetriou, L.; Pannekoek, J.N.; Wall, M.B.; Tanner, M.; Kaelen, M.; McGonigle, J.; Murphy, K.; et al. Psilocybin for Treatment-Resistant Depression: fMRI-Measured Brain Mechanisms. *Sci. Rep.* **2017**, *7*, doi:10.1038/s41598-017-13282-7.
8. Davis, A.K.; Barrett, F.S.; May, D.G.; Cosimano, M.P.; Sepeda, N.D.; Johnson, M.W.; Finan, P.H.; Griffiths, R.R. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* **2021**, *78*, 481, doi:10.1001/jamapsychiatry.2020.3285.
9. Galvão-Coelho, N.L.; Marx, W.; Gonzalez, M.; Sinclair, J.; De Manincor, M.; Perkins, D.; Sarris, J. Classic Serotonergic Psychedelics for Mood and Depressive Symptoms: A Meta-Analysis of Mood Disorder Patients and Healthy Participants. *Psychopharmacology (Berl.)* **2021**, *238*, 341–354, doi:10.1007/s00213-020-05719-1.
10. Ko, K.; Kopra, E.I.; Cleare, A.J.; Rucker, J.J. Psychedelic Therapy for Depressive Symptoms: A Systematic Review and Meta-Analysis. *J. Affect. Disord.* **2023**, *322*, 194–204, doi:10.1016/j.jad.2022.09.168.
11. Romeo, B.; Karila, L.; Martelli, C.; Benyamina, A. Efficacy of Psychedelic Treatments on Depressive Symptoms: A Meta-Analysis. *J. Psychopharmacol. (Oxf.)* **2020**, *34*, 1079–1085, doi:10.1177/0269881120919957.
12. Von Rotz, R.; Schindowski, E.M.; Jungwirth, J.; Schuldt, A.; Rieser, N.M.; Zahoranszky, K.; Seifritz, E.; Nowak, A.; Nowak, P.; Jäncke, L.; et al. Single-Dose Psilocybin-Assisted Therapy in Major Depressive Disorder: A Placebo-Controlled, Double-Blind, Randomised Clinical Trial. *eClinicalMedicine* **2023**, *56*, doi:10.1016/j.eclinm.2022.101809.
13. Van Der Meer, P.B.; Fuentes, J.J.; Kaptein, A.A.; Schoones, J.W.; De Waal, M.M.; Goudriaan, A.E.; Kramers, K.; Schellekens, A.; Somers, M.; Bossong, M.G.; et al. Therapeutic Effect of Psilocybin in Addiction: A Systematic Review. *Front. Psychiatry* **2023**, *14*, doi:10.3389/fpsyt.2023.1134454.
14. Joneborg, I.; Lee, Y.; Di, J.D.; Ceban, F.; Meshkat, S.; Lui, L.M.; Fancy, F.; Rosenblat, J.D.; Mcintyre, R.S. Active Mechanisms of Ketamine-Assisted Psychotherapy: A Systematic Review. *J. Affect. Disord.* **2022**, *315*, 105–112, doi:10.1016/j.jad.2022.07.030.
15. Agin-Liebes, G.; Haas, T.F.; Lancelotta, R.; Uthaug, M.V.; Ramaekers, J.G.; Davis, A.K. Naturalistic Use of Mescaline Is Associated with Self-Reported Psychiatric Improvements and Enduring Positive Life Changes. *ACS Pharmacol. Transl. Sci.* **2021**, *4*, 543–552, doi:10.1021/acsptsci.1c00018.
16. Agin-Liebes, G.; Zeifman, R.; Luoma, J.B.; Garland, E.L.; Campbell, W.K.; Weiss, B. Prospective Examination of the Therapeutic Role of Psychological Flexibility and Cognitive Reappraisal in the Ceremonial Use of Ayahuasca. *J. Psychopharmacol. (Oxf.)* **2022**, *36*, 295–308, doi:10.1177/02698811221080165.
17. Palhano-Fontes, F.; Barreto, D.; Onias, H.; Andrade, K.C.; Novaes, M.M.; Pessoa, J.A.; Mota-Rolim, S.A.; Osório, F.L.; Sanches, R.; Dos Santos, R.G.; et al. Rapid Antidepressant Effects of the Psychedelic Ayahuasca in Treatment-Resistant Depression: A Randomized Placebo-Controlled Trial. *Psychol. Med.* **2019**, *49*, 655–663, doi:10.1017/S0033291718001356.
18. Uthaug, M.V.; Van Oorsouw, K.; Kuypers, K.P.C.; Van Boxtel, M.; Broers, N.J.; Mason, N.L.; Toennes, S.W.; Riba, J.; Ramaekers, J.G. Sub-Acute and Long-Term Effects of Ayahuasca on Affect and Cognitive Thinking Style and Their Association with Ego Dissolution. *Psychopharmacology (Berl.)* **2018**, *235*, 2979–2989, doi:10.1007/s00213-018-4988-3.
19. Uthaug, M.V.; Davis, A.K.; Haas, T.F.; Davis, D.; Dolan, S.B.; Lancelotta, R.; Timmermann, C.; Ramaekers, J.G. The Epidemiology of Mescaline Use: Pattern of Use, Motivations for Consumption, and Perceived Consequences, Benefits, and Acute and Enduring Subjective Effects. *J. Psychopharmacol. (Oxf.)* **2022**, *36*, 309–320, doi:10.1177/02698811211013583.

20. Van Oorsouw, K.; Toennes, S.W.; Ramaekers, J.G. Therapeutic Effect of an Ayahuasca Analogue in Clinically Depressed Patients: A Longitudinal Observational Study. *Psychopharmacology (Berl.)* **2022**, *239*, 1839–1852, doi:10.1007/s00213-021-06046-9.
21. Breeksema, J.J.; Niemeijer, A.; Kuin, B.; Veraart, J.; Vermetten, E.; Kamphuis, J.; Brink, W.V.D.; Schoevers, R. Phenomenology and Therapeutic Potential of Patient Experiences during Oral Esketamine Treatment for Treatment-Resistant Depression: An Interpretative Phenomenological Study. *Psychopharmacology (Berl.)* **2023**, *240*, 1547–1560, doi:10.1007/s00213-023-06388-6.
22. Van Elk, M.; Yaden, D.B. Pharmacological, Neural, and Psychological Mechanisms Underlying Psychedelics: A Critical Review. *Neurosci. Biobehav. Rev.* **2022**, *140*, doi:10.1016/j.neubiorev.2022.104793.
23. Moreton, S.G.; Szalla, L.; Menzies, R.E.; Arena, A.F. Embedding Existential Psychology within Psychedelic Science: Reduced Death Anxiety as a Mediator of the Therapeutic Effects of Psychedelics. *Psychopharmacology (Berl.)* **2020**, *237*, 21–32, doi:10.1007/s00213-019-05391-0.
24. Nikolaidis, A.; Lancelotta, R.; Gukasyan, N.; Griffiths, R.R.; Barrett, F.S.; Davis, A.K. Subtypes of the Psychedelic Experience Have Reproducible and Predictable Effects on Depression and Anxiety Symptoms. *J. Affect. Disord.* **2022**, *324*, 239–249, doi:10.1016/j.jad.2022.12.042.
25. Roseman, L.; Nutt, D.J.; Carhart-Harris, R.L. Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. *Front. Pharmacol.* **2018**, *8*, 974, doi:10.3389/fphar.2017.00974.
26. Tulver, K.; Kaup, K.K.; Laukkonen, R.; Aru, J. Restructuring Insight: An Integrative Review of Insight in Problem-Solving, Meditation, Psychotherapy, Delusions and Psychedelics. *Conscious. Cogn.* **2023**, *110*, doi:10.1016/j.concog.2023.103494.
27. MacLean, K.A.; Johnson, M.W.; Griffiths, R.R. Mystical Experiences Ooccasioned by the Hallucinogen Psilocybin Lead to Increases in the Personality Domain of Openness. *J. Psychopharmacol. (Oxf.)* **2011**, *25*, doi:10.1177/0269881111420188.
28. Hanna, F.J.; Giordano, F.; Dupuy, P.; Puhakka, K. Agency and Transcendence: The Experience of Therapeutic Change. *Humanist. Psychol.* **1995**, *23*, 139–160, doi:10.1080/08873267.1995.9986822.
29. Schenberg, E.E. Psychedelic-Assisted Psychotherapy: A Paradigm Shift in Psychiatric Research and Development. *Front. Pharmacol.* **2018**, *9*, doi:10.3389/fphar.2018.00733.
30. Brodie, B.B.; Shore, P.A. A Concept For a Role of Serotonin and Norepinephrine as Chemical Mediators in the Brain. *Ann. N. Y. Acad. Sci.* **1957**, *66*, 631–642, doi:10.1111/j.1749-6632.1957.tb40753.x.
31. Woolley, D.W.; Shaw, E. Some Neurophysiological Aspects of Serotonin. *Br. Med. J.* **1954**, *2*, 122–126, doi:10.1136/bmj.2.4880.122.
32. Johnson, M.W.; Hendricks, P.S.; Barrett, F.S.; Griffiths, R.R. Classic Psychedelics: An Integrative Review of Epidemiology, Therapeutics, Mystical Experience, and Brain Network Function. *Pharmacol. Ther.* **2019**, *197*, 83–102, doi:10.1016/j.pharmthera.2018.11.010.
33. De Vos, C.M.H.; Mason, N.L.; Kuypers, K.P.C. Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. *Front. Psychiatry* **2021**, *12*, doi:10.3389/fpsyt.2021.724606.
34. Jaster, A.M.; González-Maeso, J. Mechanisms and Molecular Targets Surrounding the Potential Therapeutic Effects of Psychedelics. *Mol. Psychiatry* **2023**, *28*, 3595–3612, doi:10.1038/s41380-023-02274-x.
35. Brunoni, A.R.; Lopes, M.; Fregni, F. A Systematic Review and Meta-Analysis of Clinical Studies on Major Depression and BDNF Levels: Implications for the Role of Neuroplasticity in Depression. *Int. J. Neuropsychopharmacol.* **2008**, *11*, 1169–1180, doi:10.1017/S1461145708009309.
36. Belser, A.B.; Agin-Liebes, G.; Swift, T.C.; Terrana, S.; Devenot, N.; Friedman, H.L.; Guss, J.; Bossis, A.; Ross, S. Patient Experiences of Psilocybin-Assisted Psychotherapy: An Interpretative Phenomenological Analysis. *J. Humanist. Psychol.* **2017**, *57*, 354–388, doi:10.1177/0022167817706884.
37. Barrett, F.S.; Griffiths, R.R. Classic Hallucinogens and Mystical Experiences: Phenomenology and Neural Correlates. In *Behavioral Neurobiology of Psychedelic Drugs*; Halberstadt, A.L., Vollenweider, F.X., Nichols, D.E., Eds.; Current Topics in Behavioral Neurosciences; Springer Berlin Heidelberg: Berlin, Heidelberg, 2017; Vol. 36, pp. 393–430 ISBN 978-3-662-55878-2.
38. Carhart-Harris, R.L.; Kaelen, M.; Whalley, M.G.; Bolstridge, M.; Feilding, A.; Nutt, D.J. LSD Enhances Suggestibility in Healthy Volunteers. *Psychopharmacology (Berl.)* **2015**, *232*, 785–794, doi:10.1007/s00213-014-3714-z.
39. Preller, K.H.; Herdener, M.; Pokorny, T.; Planzer, A.; Kraehenmann, R.; Stämpfli, P.; Liechti, M.E.; Seifritz, E.; Vollenweider, F.X. The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. *Curr. Biol.* **2017**, *27*, 451–457, doi:10.1016/j.cub.2016.12.030.
40. Winkelman, M.J. The Mechanisms of Psychedelic Visionary Experiences: Hypotheses from Evolutionary Psychology. *Front. Neurosci.* **2017**, *11*, doi:10.3389/fnins.2017.00539.
41. Swanson, L.R. Unifying Theories of Psychedelic Drug Effects. *Front. Pharmacol.* **2018**, *9*, doi:10.3389/fphar.2018.00172.

42. Raison, C.L.; Sanacora, G.; Woolley, J.; Heinzerling, K.; Dunlop, B.W.; Brown, R.T.; Kakar, R.; Hassman, M.; Trivedi, R.P.; Robison, R.; et al. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. *JAMA* **2023**, *330*, 843–853, doi:10.1001/jama.2023.14530.
43. Davis, A.K.; So, S.; Lancelotta, R.; Barsuglia, J.P.; Griffiths, R.R. 5-Methoxy- *N,N* -Dimethyltryptamine (5-MeO-DMT) Used in a Naturalistic Group Setting Is Associated with Unintended Improvements in Depression and Anxiety. *Am. J. Drug Alcohol Abuse* **2019**, *45*, 161–169, doi:10.1080/00952990.2018.1545024.
44. Griffiths, R.R.; Johnson, M.W.; Carducci, M.A.; Umbricht, A.; Richards, W.A.; Richards, B.D.; Cosimano, M.P.; Klinedinst, M.A. Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial. *J. Psychopharmacol. (Oxf.)* **2016**, *30*, 1181–1197, doi:10.1177/0269881116675513.
45. Moreton, S.G.; Arena, A.F.A.; Foy, Y.; Menzies, R.E. Reduced Death Anxiety as a Mediator of the Relationship between Acute Subjective Effects of Psychedelics and Improved Subjective Well-Being. *Death Stud.* **2023**, *47*, 1115–1126, doi:10.1080/07481187.2023.2169848.
46. Garcia-Romeu, A.; Davis, A.K.; Erowid, F.; Erowid, E.; Griffiths, R.R.; Johnson, M.W. Cessation and Reduction in Alcohol Consumption and Misuse after Psychedelic Use. *J. Psychopharmacol. (Oxf.)* **2019**, *33*, 1088–1101, doi:10.1177/0269881119845793.
47. Davis, A.K.; Xin, Y.; Sepeda, N.D.; Garcia-Romeu, A.; Williams, M.T. Increases in Psychological Flexibility Mediate Relationship Between Acute Psychedelic Effects and Decreases in Racial Trauma Symptoms Among People of Color. *Chronic Stress* **2021**, *5*, doi:10.1177/24705470211035607.
48. Doss, M.K.; Považan, M.; Rosenberg, M.D.; Sepeda, N.D.; Davis, A.K.; Finan, P.H.; Smith, G.S.; Pekar, J.J.; Barker, P.B.; Griffiths, R.R.; et al. Psilocybin Therapy Increases Cognitive and Neural Flexibility in Patients with Major Depressive Disorder. *Transl. Psychiatry* **2021**, *11*, doi:10.1038/s41398-021-01706-y.
49. Gandy, S. Predictors and Potentiators of Psychedelicoccasioned Mystical Experiences. *J. Psychedelic Stud.* **2022**, *6*, 31–47, doi:10.1556/2054.2022.00198.
50. Griffiths, R.; Richards, W.; Johnson, M.; McCann, U.; Jesse, R. Mystical-Type Experiences Occasioned by Psilocybin Mediate the Attribution of Personal Meaning and Spiritual Significance 14 Months Later. *J. Psychopharmacol. (Oxf.)* **2008**, *22*, 621–632, doi:10.1177/0269881108094300.
51. Griffiths, R.R.; Johnson, M.W.; Richards, W.A.; Richards, B.D.; Jesse, R.; MacLean, K.A.; Barrett, F.S.; Cosimano, M.P.; Klinedinst, M.A. Psilocybin-Occasioned Mystical-Type Experience in Combination with Meditation and Other Spiritual Practices Produces Enduring Positive Changes in Psychological Functioning and in Trait Measures of Prosocial Attitudes and Behaviors. *J. Psychopharmacol. (Oxf.)* **2018**, *32*, 49–69, doi:10.1177/0269881117731279.
52. Yazar-Klosinski, B.B.; Mithoefer, M.C. Potential Psychiatric Uses for MDMA. *Clin. Pharmacol. Ther.* **2016**, *101*, doi:10.1002/cpt.565.
53. Barksdale, B.R.; Doss, M.K.; Fonzo, G.A.; Nemeroff, C.B. The Mechanistic Divide in Psychedelic Neuroscience: An Unbridgeable Gap? *Neurotherapeutics* **2024**, *21*, doi:10.1016/j.neurot.2024.e00322.
54. Gorman, I.; Belser, A.B.; Jerome, L.; Hennigan, C.; Shechet, B.; Hamilton, S.; Yazar-Klosinski, B.; Emerson, A.; Feduccia, A.A. Posttraumatic Growth After MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. *J. Trauma. Stress* **2020**, *33*, doi:10.1002/jts.22479.
55. Wilkinson, S.T.; Rhee, T.G.; Joormann, J.; Webler, R.; Ortiz Lopez, M.; Kitay, B.; Fasula, M.; Elder, C.; Fenton, L.; Sanacora, G. Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. *Psychother. Psychosom.* **2021**, *90*, 318–327, doi:10.1159/000517074.
56. Earleywine, M.; Ueno, L.F.; Mian, M.N.; Altman, B.R. Cannabis-Induced Oceanic Boundlessness. *J. Psychopharmacol. (Oxf.)* **2021**, *35*, 841–847, doi:10.1177/0269881121997099.
57. Earleywine, M.; Mian, M.N.; Altman, B.R.; Leo, J.A.D. Expectancies for Cannabis-Induced Emotional Breakthrough, Mystical Experiences and Changes in Dysfunctional Attitudes: Perceptions of the Potential for Cannabis-Assisted Psychotherapy for Depression. *Cannabis* **2022**, *5*, doi:10.26828/cannabis/2022.02.02.
58. Farmer, S.; Slavin, M.N.; Loflin, M.J.E.; Luba, R.; Earleywine, M. Aversiveness and Meaningfulness of Uncomfortable Experiences with Edible Cannabis. *J. Psychoactive Drugs* **2019**, *51*, 413–420, doi:10.1080/02791072.2019.1645371.
59. Ferrara, M.S. Peak-Experience and the Entheogenic Use of Cannabis in World Religions. *J. Psychedelic Stud.* **2020**, *4*, 179–191, doi:10.1556/2054.2020.00122.
60. Breeksema, J.J.; Niemeijer, A.; Kuin, B.; Veraart, J.; Kamphuis, J.; Schimmel, N.; Van Den Brink, W.; Vermetten, E.; Schoevers, R. Holding on or Letting Go? Patient Experiences of Control, Context, and Care in Oral Esketamine Treatment for Treatment-Resistant Depression: A Qualitative Study. *Front. Psychiatry* **2022**, *13*, doi:10.3389/fpsyt.2022.948115.
61. Aday, J.S.; Davis, A.K.; Mitzkovitz, C.M.; Bloesch, E.K.; Davoli, C.C. Predicting Reactions to Psychedelic Drugs: A Systematic Review of States and Traits Related to Acute Drug Effects. *ACS Pharmacol. Transl. Sci.* **2021**, *4*, 424–435, doi:10.1021/acsptsci.1c00014.

62. Kaelen, M.; Giribaldi, B.; Raine, J.; Evans, L.; Timmerman, C.; Rodriguez, N.; Roseman, L.; Feilding, A.; Nutt, D.; Carhart-Harris, R. The Hidden Therapist: Evidence for a Central Role of Music in Psychedelic Therapy. *Psychopharmacology (Berl.)* **2018**, *235*, 505–519, doi:10.1007/s00213-017-4820-5.
63. Carhart-Harris, R.L.; Roseman, L.; Haijen, E.; Erritzoe, D.; Watts, R.; Branchi, I.; Kaelen, M. Psychedelics and the Essential Importance of Context. *J. Psychopharmacol. (Oxf.)* **2018**, *32*, 725–731, doi:10.1177/0269881118754710.
64. Bohn, A.; Kiggen, M.H.H.; Uthaug, M.V.; Van Oorsouw, K.I.M.; Ramaekers, J.G.; Van Schie, H.T. Altered States of Consciousness During Ceremonial San Pedro Use. *Int. J. Psychol. Relig.* **2023**, *33*, 309–331, doi:10.1080/10508619.2022.2139502.
65. Winkelman, M. Psychedelics as Medicines for Substance Abuse Rehabilitation: Evaluating Treatments with LSD, Peyote, Ibogaine and Ayahuasca. *Curr. Drug Abuse Rev.* **2015**, *7*, 101–116, doi:10.2174/1874473708666150107120011.
66. Richards, W.A. Psychedelic Psychotherapy: Insights From 25 Years of Research. *J. Humanist. Psychol.* **2017**, *57*, 323–337, doi:10.1177/0022167816670996.
67. Elkins, D.N. Common Factors: What Are They and What Do They Mean for Humanistic Psychology? *J. Humanist. Psychol.* **2022**, *62*, 21–30, doi:10.1177/0022167819858533.
68. Krupnick, J.L.; Sotsky, S.M.; Simmens, S.; Moyer, J.; Elkin, I.; Watkins, J.; Pilkonis, P.A. The Role of the Therapeutic Alliance in Psychotherapy and Pharmacotherapy Outcome: Findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J. Consult. Clin. Psychol.* **1996**, *64*, 532–539, doi:10.1037/0022-006X.64.3.532.
69. Weiss, M.; Gaston, L.; Propst, A.; Wisebord, S.; Zicherman, V. The Role of the Alliance in the Pharmacologic Treatment of Depression. *J. Clin. Psychiatry* **1997**, *58*, 196–204, doi:10.4088/JCP.v58n0504.
70. Maia, L.O.; Daldegan-Bueno, D.; Wießner, I.; Araujo, D.B.; Tófoli, L.F. Ayahuasca's Therapeutic Potential: What We Know – and What Not. *Eur. Neuropsychopharmacol.* **2023**, *66*, 45–61, doi:10.1016/j.euroneuro.2022.10.008.
71. Palhano-Fontes, F.; Soares, B.L.; Galvão-Coelho, N.L.; Arcoverde, E.; Araujo, D.B. Ayahuasca for the Treatment of Depression. In *Disruptive Psychopharmacology*; Barrett, F.S., Preller, K.H., Eds.; Current Topics in Behavioral Neurosciences; Springer International Publishing: Cham, 2021; Vol. 56, pp. 113–124 ISBN 978-3-031-12183-8.
72. Sanches, R.F.; De Lima Osório, F.; Dos Santos, R.G.; Macedo, L.R.H.; Maia-de-Oliveira, J.P.; Wichert-Ana, L.; De Araujo, D.B.; Riba, J.; Crippa, J.A.S.; Hallak, J.E.C. Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression: A SPECT Study. *J. Clin. Psychopharmacol.* **2016**, *36*, 77–81, doi:10.1097/JCP.0000000000000436.
73. Dos Santos, R.G.; Osório, F.L.; Crippa, J.A.S.; Riba, J.; Zuardi, A.W.; Hallak, J.E.C. Antidepressive, Anxiolytic, and Antiaddictive Effects of Ayahuasca, Psilocybin and Lysergic Acid Diethylamide (LSD): A Systematic Review of Clinical Trials Published in the Last 25 Years. *Ther. Adv. Psychopharmacol.* **2016**, *6*, 193–213, doi:10.1177/2045125316638008.
74. Santos, R.G.; Landeira-Fernandez, J.; Strassman, R.J.; Motta, V.; Cruz, A.P.M. Effects of Ayahuasca on Psychometric Measures of Anxiety, Panic-like and Hopelessness in Santo Daime Members. *J. Ethnopharmacol.* **2007**, *112*, 507–513, doi:10.1016/j.jep.2007.04.012.
75. Barbosa, P.C.R.; Strassman, R.J.; Da Silveira, D.X.; Areco, K.; Hoy, R.; Pommy, J.; Thoma, R.; Bogenschutz, M. Psychological and Neuropsychological Assessment of Regular Hoasca Users. *Compr. Psychiatry* **2016**, *71*, 95–105, doi:10.1016/j.comppsych.2016.09.003.
76. Vamvakopoulou, I.A.; Narine, K.A.D.; Campbell, I.; Dyck, J.R.B.; Nutt, D.J. Mescaline: The Forgotten Psychedelic. *Neuropharmacology* **2023**, *222*, doi:10.1016/j.neuropharm.2022.109294.
77. Köck, P.; Froelich, K.; Walter, M.; Lang, U.; Dürsteler, K.M. A Systematic Literature Review of Clinical Trials and Therapeutic Applications of Ibogaine. *J. Subst. Abuse Treat.* **2021**, *138*, doi:10.1016/j.jsat.2021.108717.
78. Schenberg, E.E.; Comis, M.A.D.C.; Felipe, J.; Alexandre, M.; Tófoli, L.F.; Daniel, B.; Chaves, R.; Silveira, D.X.D.; Ekman, E.; Instituto, S.; et al. A Phenomenological Analysis of the Subjective Experience Elicited by Ibogaine in the Context of a Drug Dependence Treatment. *J. Psychedelic Stud.* **2017**, *1*, 74–83, doi:10.1556/2054.01.2017.007.
79. Cameron, L.P.; Tombari, R.J.; Lu, J.; Pell, A.J.; Hurley, Z.Q.; Ehinger, Y.; Vargas, M.V.; Mccarroll, M.N.; Taylor, J.C.; Myers-Turnbull, D.; et al. A Non-Hallucinogenic Psychedelic Analog with Therapeutic Potential. *Nature* **2021**, *589*, 474–479, doi:10.1038/s41586-020-3008-z.
80. Tupper, K.W. Ayahuasca Healing beyond the Amazon: The Globalization of a Traditional Indigenous Entheogenic Practice. *Glob. Netw.* **2009**, *9*, 117–136, doi:10.1111/j.1471-0374.2009.00245.x.
81. Dobkin De Rios, M. Drug Tourism in the Amazon. *Anthropol. Conscious.* **1994**, *5*, 16–19, doi:10.1525/ac.1994.5.1.16.

82. Timmermann, C.; Watts, R.; Dupuis, D. Towards Psychedelic Apprenticeship: Developing a Gentle Touch for the Mediation and Validation of Psychedelic-Induced Insights and Revelations. *Transcult. Psychiatry* **2022**, *59*, 691–704, doi:10.1177/13634615221082796.
83. Olson, D.E. The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effects. *ACS Pharmacol. Transl. Sci.* **2021**, *4*, 563–567, doi:10.1021/acsptsci.0c00192.
84. Yaden, D.B.; Griffiths, R.R. The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. *ACS Pharmacol. Transl. Sci.* **2020**, *4*, 568–572, doi:10.1021/acsptsci.0c00194.
85. Letheby, C. *Philosophy of Psychedelics*; International perspectives in philosophy & psychology; Oxford University Press: New York, 2021; ISBN 978-0-19-884312-2.
86. Griffiths, R.R.; Richards, W.A.; McCann, U.; Jesse, R. Psilocybin Can Occasion Mystical-Type Experiences Having Substantial and Sustained Personal Meaning and Spiritual Significance. *Psychopharmacology (Berl.)* **2006**, *187*, 268–283, doi:10.1007/s00213-006-0457-5.
87. Griffiths, R.R.; Johnson, M.W.; Richards, W.A.; Richards, B.D.; McCann, U.; Jesse, R. Psilocybin Occasioned Mystical-Type Experiences: Immediate and Persisting Dose-Related Effects. *Psychopharmacology (Berl.)* **2011**, *218*, 649–665, doi:10.1007/s00213-011-2358-5.
88. Schmid, Y.; Gasser, P.; Oehen, P.; Liechti, M.E. Acute Subjective Effects in LSD-and MDMA-Assisted Psychotherapy. *J. Psychopharmacol. (Oxf.) 35*, 362–374, doi:10.1177/0269881120959604.
89. Ross, S. Therapeutic Use of Classic Psychedelics to Treat Cancer-Related Psychiatric Distress. *Int. Rev. Psychiatry* **2018**, *30*, 317–330, doi:10.1080/09540261.2018.1482261.
90. Eyerman, J. A Clinical Report of Holotropic Breathwork in 11,000 Psychiatric Inpatients in a Community Hospital Setting. *MAPS Bull. Spec. Ed.* **2013**, *23*, 24–27.
91. Fincham, G.W.; Kartar, A.; Uthaug, M.V.; Anderson, B.; Hall, L.; Nagai, Y.; Critchley, H.; Colasanti, A. High Ventilation Breathwork Practices: An Overview of Their Effects, Mechanisms, and Considerations for Clinical Applications. *Neurosci. Biobehav. Rev.* **2023**, *155*, doi:10.1016/j.neubiorev.2023.105453.
92. Fritz, P.; Lejeune, N.; Cardone, P.; Gosseries, O.; Martial, C. Bridging the Gap: (A)Typical Psychedelic and near-Death Experience Insights. *Curr. Opin. Behav. Sci.* **2024**, *55*, doi:10.1016/j.cobeha.2023.101349.
93. Holas, P.; Kamińska, J. Mindfulness Meditation and Psychedelics: Potential Synergies and Commonalities. *Pharmacol. Rep.* **2023**, *75*, 1398–1409, doi:10.1007/s43440-023-00551-8.
94. Lyon, A. *Psychedelic Experience: Revealing the Mind*; 1st ed.; Oxford University Press: New York, 2023; ISBN 978-0-19-884375-7.
95. Osmond, H. A Review of the Clinical Effects of Psychotomimetic Agents. *Ann. N. Y. Acad. Sci.* **1957**, *66*, 418–434, doi:10.1111/j.1749-6632.1957.tb40738.x.
96. Brown, R.P.; Gerbarg, P.L.; Muench, F. Breathing Practices for Treatment of Psychiatric and Stress-Related Medical Conditions. *Psychiatr. Clin. North Am.* **2013**, *36*, 121–140, doi:10.1016/j.psc.2013.01.001.
97. Stenkamp, K.; Palva, J.M.; Uusisaari, M.; Schuchmann, S.; Schmitz, D.; Heinemann, U.; Kaila, K. Enhanced Temporal Stability of Cholinergic Hippocampal Gamma Oscillations Following Respiratory Alkalosis In Vitro. *J. Neurophysiol.* **2001**, *85*, 2063–2069, doi:10.1152/jn.2001.85.5.2063.
98. Li, S.; Rymer, W.Z. Voluntary Breathing Influences Corticospinal Excitability of Nonrespiratory Finger Muscles. *J. Neurophysiol.* **2011**, *105*, 512–521, doi:10.1152/jn.00946.2010.
99. Sun, Y.-G.; Wu, C.-S.; Renger, J.J.; Uebele, V.N.; Lu, H.-C.; Beierlein, M. GABAergic Synaptic Transmission Triggers Action Potentials in Thalamic Reticular Nucleus Neurons. *J. Neurosci.* **2012**, *32*, 7782–7790, doi:10.1523/JNEUROSCI.0839-12.2012.
100. Agadzhanyan, N.A.; Panina, M.I.; Kozupitsa, G.S.; Sergeev, O.S. Subjective and Neurological Manifestations of Hyperventilation States of Different Intensities. *Hum. Physiol.* **2003**, *29*, 448–452, doi:10.1023/A:1024929523667.
101. Puente, I. Holotropic Breathwork Can Occasion Mystical Experiences in the Context of a Daylong Workshop. *J. Transpers. Res.* **2014**, *6*, 40–50.
102. De Wit, P.A.J.M.; Moraes Cruz, R. Treating PTSD with Connected Breathing: A Clinical Case Study and Theoretical Implications. *Eur. J. Trauma Dissociation* **2021**, *5*, doi:10.1016/j.ejtd.2020.100152.
103. Uthaug, M.V.; Mason, N.L.; Havenith, M.N.; Vancura, M.; Ramaekers, J.G. An Experience with Holotropic Breathwork Is Associated with Improvement in Non-Judgement and Satisfaction with Life While Reducing Symptoms of Stress in a Czech-Speaking Population. *J. Psychedelic Stud.* **2022**, *5*, 176–189, doi:10.1556/2054.2021.00193.
104. Khubsing, R.S.I.; Leerdam, M.V.; Haijen, E.C.H.M.; Kuypers, K.P.C. Self-Rated Effectiveness of Ayahuasca and Breathwork on Well-Being, Psychological Resilience, Self-Compassion, and Personality: An Observational Comparison Study. *Psychoactives* **2024**, *3*, 167–183, doi:10.3390/psychoactives3020011.
105. Lebedev, A.V.; Lövdén, M.; Rosenthal, G.; Feilding, A.; Nutt, D.J.; Carhart-Harris, R.L. Finding the Self by Losing the Self: Neural Correlates of Ego-Dissolution under Psilocybin: Finding the Self by Losing the Self. *Hum. Brain Mapp.* **2015**, *36*, 3137–3153, doi:10.1002/hbm.22833.
106. Millière, R.; Carhart-Harris, R.L.; Roseman, L.; Trautwein, F.-M.; Berkovich-Ohana, A. Psychedelics, Meditation, and Self-Consciousness. *Front. Psychol.* **2018**, *9*, doi:10.3389/fpsyg.2018.01475.

107. Simonsson, O.; Goldberg, S.B. Linkages between Psychedelics and Meditation in a Population-Based Sample in the United States. *J. Psychoactive Drugs* **2023**, *55*, 11–18, doi:10.1080/02791072.2021.2022816.
108. Brewer, J.A.; Worhunsky, P.D.; Gray, J.R.; Tang, Y.-Y.; Weber, J.; Kober, H. Meditation Experience Is Associated with Differences in Default Mode Network Activity and Connectivity. *Proc. Natl. Acad. Sci.* **2011**, *108*, 20254–20259, doi:10.1073/pnas.1112029108.
109. Carhart-Harris, R.L.; Erritzoe, D.; Williams, T.; Stone, J.M.; Reed, L.J.; Colasanti, A.; Tyacke, R.J.; Leech, R.; Malizia, A.L.; Murphy, K.; et al. Neural Correlates of the Psychedelic State as Determined by fMRI Studies with Psilocybin. *Proc. Natl. Acad. Sci.* **2012**, *109*, 2138–2143, doi:10.1073/pnas.1119598109.
110. Farb, N.A.S.; Segal, Z.V.; Mayberg, H.; Bean, J.; McKeon, D.; Fatima, Z.; Anderson, A.K. Attending to the Present: Mindfulness Meditation Reveals Distinct Neural Modes of Self-Reference. *Soc. Cogn. Affect. Neurosci.* **2007**, *2*, 313–322, doi:10.1093/scan/nsm030.
111. Dahl, C.J.; Lutz, A.; Davidson, R.J. Reconstructing and Deconstructing the Self: Cognitive Mechanisms in Meditation Practice. *Trends Cogn. Sci.* **2015**, *19*, 515–523, doi:10.1016/j.tics.2015.07.001.
112. Van Lente, E.; Hogan, M.J. Understanding the Nature of Oneness Experience in Meditators Using Collective Intelligence Methods. *Front. Psychol.* **2020**, *11*, 2092, doi:10.3389/fpsyg.2020.02092.
113. Bærentsen, K.B.; Stødkilde-Jørgensen, H.; Sommerlund, B.; Hartmann, T.; Damsgaard-Madsen, J.; Fosnæs, M.; Green, A.C. An Investigation of Brain Processes Supporting Meditation. *Cogn. Process.* **2010**, *11*, 57–84, doi:10.1007/s10339-009-0342-3.
114. Mills, P.J.; Peterson, C.T.; Pung, M.A.; Patel, S.; Weiss, L.; Wilson, K.L.; Doraiswamy, P.M.; Martin, J.A.; Tanzi, R.E.; Chopra, D. Change in Sense of Nondual Awareness and Spiritual Awakening in Response to a Multidimensional Well-Being Program. *J. Altern. Complement. Med.* **2018**, *24*, 343–351, doi:10.1089/acm.2017.0160.
115. Lilly, J.C. *The Deep Self: Consciousness Exploration in the Isolation Tank*; Consciousness classics; Gateways Books and Tapes: Nevada City, CA, 2007; ISBN 978-0-89556-116-9.
116. Kjellgren, A.; Lyden, F.; Norlander, T. Sensory Isolation in Flotation Tanks: Altered States of Consciousness and Effects on Well-Being. *Qual. Rep.* **2008**, *13*, 636–656, doi:10.46743/2160-3715/2008.1577.
117. Norlander, T.; Kjellgren, A.; Archer, T. Effects of Flotation-Versus Chamber-Restricted Environmental Stimulation Technique (Rest) on Creativity and Realism under Stress and Non-Stress Conditions. *Imagin. Cogn. Personal.* **2003**, *22*, 343–359, doi:10.2190/0LAE-M7WP-R6UQ-CR3P.
118. Dotan, A.; Shriki, O. Tinnitus-like "Hallucinations" Elicited by Sensory Deprivation in an Entropy Maximization Recurrent Neural Network. *PLOS Comput. Biol.* **2021**, *17*, doi:10.1371/journal.pcbi.1008664.
119. Jonsson, K.; Kjellgren, A. Characterizing the Experiences of Flotation-REST (Restricted Environmental Stimulation Technique) Treatment for Generalized Anxiety Disorder (GAD): A Phenomenological Study. *Eur. J. Integr. Med.* **2017**, *12*, 53–59, doi:10.1016/j.eujim.2017.04.011.
120. Suedfeld, P.; Landon, P.B.; Ballard, E.J. Effects of Reduced Stimulation on Divergent and Convergent Thinking. *Environ. Behav.* **1983**, *15*, 727–738, doi:10.1177/0013916583156003.
121. Suedfeld, P.; Metcalfe, J.; Bluck, S. Enhancement of Scientific Creativity by Flotation Rest (Restricted Environmental Stimulation Technique). *J. Environ. Psychol.* **1987**, *7*, 219–231, doi:10.1016/S0272-4944(87)80031-2.
122. Al Zoubi, O.; Misaki, M.; Bodurka, J.; Kuplicki, R.; Wohlrab, C.; Schoenhals, W.A.; Refai, H.H.; Khalsa, S.S.; Stein, M.B.; Paulus, M.P.; et al. Taking the Body off the Mind: Decreased Functional Connectivity between Somatomotor and Default-mode Networks Following Floatation-REST. *Hum. Brain Mapp.* **2021**, *42*, 3216–3227, doi:10.1002/hbm.25429.
123. Ko, K.; Knight, G.; Rucker, J.J.; Cleare, A.J. Psychedelics, Mystical Experience, and Therapeutic Efficacy: A Systematic Review. *Front. Psychiatry* **2022**, *13*, doi:10.3389/fpsyt.2022.917199.
124. Bogenschutz, M.P.; Forcehimes, A.A.; Pommy, J.A.; Wilcox, C.E.; Barbosa, P.; Strassman, R.J. Psilocybin-Assisted Treatment for Alcohol Dependence: A Proof-of-Concept Study. *J. Psychopharmacol. (Oxf.)* **2015**, *29*, 289–299, doi:10.1177/0269881114565144.
125. Carhart-Harris, R.L.; Erritzoe, D.; Haijen, E.; Kaelen, M.; Watts, R. Psychedelics and Connectedness. *Psychopharmacology (Berl.)* **2018**, *235*, 547–550, doi:10.1007/s00213-017-4701-y.
126. Hartogsohn, I. The Meaning-Enhancing Properties of Psychedelics and Their Mediator Role in Psychedelic Therapy, Spirituality, and Creativity. *Front. Neurosci.* **2018**, *12*, doi:10.3389/fnins.2018.00129.
127. Van Den Hurk, P.A.M.; Wingens, T.; Giommi, F.; Barendregt, H.P.; Speckens, A.E.M.; Van Schie, H.T. On the Relationship Between the Practice of Mindfulness Meditation and Personality—an Exploratory Analysis of the Mediating Role of Mindfulness Skills. *Mindfulness* **2011**, *2*, 194–200, doi:10.1007/s12671-011-0060-7.
128. Stace, W.T. *Mysticism and Philosophy*; St. Martin's Press: New York, 1960; ISBN 0-87477-416-0.
129. Barrett, F.S.; Johnson, M.W.; Griffiths, R.R. Validation of the Revised Mystical Experience Questionnaire in Experimental Sessions with Psilocybin. *J. Psychopharmacol. (Oxf.)* **2015**, *29*, 1182–1190, doi:10.1177/0269881115609019.

130. MacLean, K.A.; Leoutsakos, J.S.; Johnson, M.W.; Griffiths, R.R. Factor Analysis of the Mystical Experience Questionnaire: A Study of Experiences Occasioned by the Hallucinogen Psilocybin. *J. Sci. Study Relig.* **2012**, *51*, 721–737, doi:10.1111/j.1468-5906.2012.01685.x.
131. Lyvers, M.; Meester, M. Illicit Use of LSD or Psilocybin, but Not MDMA or Nonpsychedelic Drugs, Is Associated with Mystical Experiences in a Dose-Dependent Manner. *J. Psychoactive Drugs* **2012**, *44*, 410–417, doi:10.1080/02791072.2012.736842.
132. Isham, A.; Elf, P.; Jackson, T. Self-Transcendent Experiences as Promoters of Ecological Wellbeing? Exploration of the Evidence and Hypotheses to Be Tested. *Front. Psychol.* **2022**, *13*, doi:10.3389/fpsyg.2022.1051478.
133. Dyck, E.; Elcock, C. Reframing Bummer Trips: Scientific and Cultural Explanations to Adverse Reactions to Psychedelic Drug Use. *Soc. Hist. Alcohol Drugs* **2020**, *34*, 271–296, doi:10.1086/707512.
134. Gashi, L.; Sandberg, S.; Pedersen, W. Making "Bad Trips" Good: How Users of Psychedelics Narratively Transform Challenging Trips into Valuable Experiences. *Int. J. Drug Policy* **2021**, *87*, 102997, doi:10.1016/j.drugpo.2020.102997.
135. Gasser, P.; Kirchner, K.; Passie, T. LSD-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Disease: A Qualitative Study of Acute and Sustained Subjective Effects. *J. Psychopharmacol. (Oxf.)* **2015**, *29*, 57–68, doi:10.1177/0269881114555249.
136. Timmermann, C.; Roseman, L.; Williams, L.; Erritzoe, D.; Martial, C.; Cassol, H.; Laureys, S.; Nutt, D.; Carhart-Harris, R. DMT Models the Near-Death Experience. *Front. Psychol.* **2018**, *9*, doi:10.3389/fpsyg.2018.01424.
137. Krupitsky, E.; Burakov, A.; Romanova, T.; Dunaevsky, I.; Strassman, R.; Grinenko, A. Ketamine Psychotherapy for Heroin Addiction: Immediate Effects and Two-Year Follow-Up. *J. Subst. Abuse Treat.* **2002**, *23*, 273–283, doi:10.1016/S0740-5472(02)00275-1.
138. Van Lommel, P.; Van Wees, R.; Meyers, V.; Elfferich, I. Near-Death Experience in Survivors of Cardiac Arrest: A Prospective Study in the Netherlands. *The Lancet* **2001**, *358*, 2039–2045, doi:10.1016/S0140-6736(01)07100-8.
139. Hendricks, P.S. Awe: A Putative Mechanism Underlying the Effects of Classic Psychedelic-Assisted Psychotherapy. *Int. Rev. Psychiatry* **2018**, *30*, 331–342, doi:10.1080/09540261.2018.1474185.
140. Keltner, D.; Haidt, J. Approaching Awe, a Moral, Spiritual, and Aesthetic Emotion. *Cogn. Emot.* **2003**, *17*, 297–314, doi:10.1080/02699930302297.
141. Van Elk, M.; Arciniegas Gomez, M.A.; Van Der Zwaag, W.; Van Schie, H.T.; Sauter, D. The Neural Correlates of the Awe Experience: Reduced Default Mode Network Activity during Feelings of Awe. *Hum. Brain Mapp.* **2019**, *40*, 3561–3574, doi:10.1002/hbm.24616.
142. Chen, S.K.; Mongrain, M. Awe and the Interconnected Self. *J. Posit. Psychol.* **2021**, *16*, 770–778, doi:10.1080/17439760.2020.1818808.
143. Shiota, M.N.; Keltner, D.; Mossman, A. The Nature of Awe: Elicitors, Appraisals, and Effects on Self-Concept. *Cogn. Emot.* **2007**, *21*, 944–963, doi:10.1080/02699930600923668.
144. Van Cappellen, P.; Saroglou, V. Awe Activates Religious and Spiritual Feelings and Behavioral Intentions. *Psychol. Relig. Spiritual.* **2012**, *4*, 223–236, doi:10.1037/a0025986.
145. Lutkajtis, A. Entity Encounters and the Therapeutic Effect of the Psychedelic Mystical Experience. *J. Psychedelic Stud.* **2021**, *4*, 171–178, doi:10.1556/2054.2020.00143.
146. Rudd, M.; Vohs, K.D.; Aaker, J. Awe Expands People's Perception of Time, Alters Decision Making, and Enhances Well-Being. *Psychol. Sci.* **2012**, *23*, 1130–1136, doi:10.1177/0956797612438731.
147. Anderson, C.L.; Monroy, M.; Keltner, D. Awe in Nature Heals: Evidence from Military Veterans, at-Risk Youth, and College Students. *Emotion* **2018**, *18*, 1195–1202, doi:10.1037/emo0000442.
148. Rivera, G.N.; Vess, M.; Hicks, J.A.; Routledge, C. Awe and Meaning: Elucidating Complex Effects of Awe Experiences on Meaning in Life. *Eur. J. Soc. Psychol.* **2020**, *50*, 392–405, doi:10.1002/ejsp.2604.
149. Nour, M.M.; Carhart-Harris, R.L.; Bch, B.M. Psychedelics and the Science of Self Experience. *Br. J. Psychiatry* **2017**, *210*, 177–179, doi:10.1192/bjp.bp.116.194738.
150. Davis, A.K.; Clifton, J.M.; Weaver, E.G.; Hurwitz, E.S.; Johnson, M.W.; Griffiths, R.R. Survey of Entity Encounter Experiences Occasioned by Inhaled *N,N* -Dimethyltryptamine: Phenomenology, Interpretation, and Enduring Effects. *J. Psychopharmacol. (Oxf.)* **2020**, *34*, 1008–1020, doi:10.1177/0269881120916143.
151. Timmermann, C.; Kettner, H.; Letheby, C.; Roseman, L.; Rosas, F.E.; Carhart-Harris, R.L. Psychedelics Alter Metaphysical Beliefs. *Sci. Rep.* **2021**, *11*, doi:10.1038/s41598-021-01209-2.
152. Carhart-Harris, R.L.; Friston, K.J. REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacol. Rev.* **2019**, *71*, 316–344, doi:10.1124/pr.118.017160.
153. Van Eyghen, H. Psychedelics and the Entropic Brain Beyond the Self. *Int. J. Psychol. Relig.* **2023**, *33*, 277–293, doi:10.1080/10508619.2023.2192078.
154. Carhart-Harris, R.L.; Leech, R.; Hellyer, P.J.; Shanahan, M.; Feilding, A.; Tagliazucchi, E.; Chialvo, D.R.; Nutt, D. The Entropic Brain: A Theory of Conscious States Informed by Neuroimaging Research with Psychedelic Drugs. *Front. Hum. Neurosci.* **2014**, *8*, doi:10.3389/fnhum.2014.00020.

155. Girn, M.; Rosas, F.E.; Daws, R.E.; Gallen, C.L.; Gazzaley, A.; Carhart-Harris, R.L. A Complex Systems Perspective on Psychedelic Brain Action. *Trends Cogn. Sci.* **2023**, *27*, 433–445, doi:10.1016/j.tics.2023.01.003.
156. Watts, A. *The Joyous Cosmology: Adventures in the Chemistry of Consciousness*; Vintage Books: New York, 1962; ISBN 978-0-394-70299-5.
157. Garcia-Romeu, A.; Griffiths, R.; Johnson, M. Psilocybin-Occasioned Mystical Experiences in the Treatment of Tobacco Addiction. *Curr. Drug Abuse Rev.* **2015**, *7*, 157–164, doi:10.2174/1874473708666150107121331.
158. Young, W.C.; Nadarajah, S.R.; Skeath, P.R.; Berger, A.M. Spirituality in the Context of Life-Threatening Illness and Life-Transforming Change. *Palliat. Support. Care* **2015**, *13*, 653–660, doi:10.1017/S1478951514000340.
159. Smigielski, L.; Scheidegger, M.; Kometer, M.; Vollenweider, F.X. Psilocybin-Assisted Mindfulness Training Modulates Self-Consciousness and Brain Default Mode Network Connectivity with Lasting Effects. *NeuroImage* **2019**, *196*, 207–215, doi:10.1016/j.neuroimage.2019.04.009.
160. Asakage, S.; Nakano, T. The Salience Network Is Activated during Self-recognition from Both First-person and Third-person Perspectives. *Hum. Brain Mapp.* **2023**, *44*, 559–570, doi:10.1002/hbm.26084.
161. Aday, J.S.; Mitzkovitz, C.M.; Bloesch, E.K.; Davoli, C.C.; Davis, A.K. Long-Term Effects of Psychedelic Drugs: A Systematic Review. *Neurosci. Biobehav. Rev.* **2020**, *113*, 179–189, doi:10.1016/j.neubiorev.2020.03.017.
162. Low, F.; Earleywine, M. Psychedelic Experiences After Bereavement Improve Symptoms of Grief: The Influence of Emotional Breakthroughs and Challenging Experiences. *J. Psychoactive Drugs* **2024**, *56*, 316–323, doi:10.1080/02791072.2023.2228303.
163. Roseman, L.; Haijen, E.; Idialu-Ikato, K.; Kaelen, M.; Watts, R.; Carhart-Harris, R. Emotional Breakthrough and Psychedelics: Validation of the Emotional Breakthrough Inventory. *J. Psychopharmacol. (Oxf.)* **2019**, *33*, 1076–1087, doi:10.1177/0269881119855974.
164. Freud, S. *A General Introduction to Psychoanalysis*; Boni & Liveright: New York, 1920; ISBN 978-0-671-80032-1.
165. Grof, S.; Grof, C. *Holotropic Breathwork: A New Approach to Self-Exploration and Therapy*; SUNY series in transpersonal and humanistic psychology; State University of New York Press: Albany, 2010; ISBN 978-1-4384-3393-6.
166. Lindegaard, T. Do Psychedelics Facilitate Emergence of Unconscious Psychological Processes? *Psychodyn. Psychiatry* **2023**, *51*, 270–286, doi:10.1521/pdps.2023.51.3.270.
167. Jennissen, S.; Huber, J.; Ehrenthal, J.C.; Schauenburg, H.; Dinger, U. Association Between Insight and Outcome of Psychotherapy: Systematic Review and Meta-Analysis. *Am. J. Psychiatry* **2018**, *175*, 961–969, doi:10.1176/appi.ajp.2018.17080847.
168. Davis, A.K.; Barrett, F.S.; Griffiths, R.R. Psychological Flexibility Mediates the Relations between Acute Psychedelic Effects and Subjective Decreases in Depression and Anxiety. *J. Context. Behav. Sci.* **2020**, *15*, 39–45, doi:10.1016/j.jcbs.2019.11.004.
169. Noorani, T.; Garcia-Romeu, A.; Swift, T.C.; Griffiths, R.R.; Johnson, M.W. Psychedelic Therapy for Smoking Cessation: Qualitative Analysis of Participant Accounts. *J. Psychopharmacol. (Oxf.)* **2018**, *32*, 756–769, doi:10.1177/0269881118780612.
170. Danek, A.H.; Fraps, T.; Müller, A.V.; Grothe, B.; Öllinger, M. It's a Kind of Magic–What Self-Reports Can Reveal about the Phenomenology of Insight Problem Solving. *Front. Psychol.* **2014**, *5*, doi:10.3389/fpsyg.2014.01408.
171. Waldron, J.L. The Life Impact of Transcendent Experiences with a Pronounced Quality of "Noesis." *J. Transpers. Psychol.* **1998**, *30*, 103–134.
172. Agin-Liebes, G.; Ekman, E.; Anderson, B.; Malloy, M.; Haas, A.; Woolley, J. Participant Reports of Mindfulness, Posttraumatic Growth, and Social Connectedness in Psilocybin-Assisted Group Therapy: An Interpretive Phenomenological Analysis. *J. Humanist. Psychol.* **2024**, *64*, 564–591, doi:10.1177/00221678211022949.
173. Argento, E.; Capler, R.; Thomas, G.; Lucas, P.; Tupper, K.W. Exploring Ayahuasca-assisted Therapy for Addiction: A Qualitative Analysis of Preliminary Findings among an Indigenous Community in Canada. *Drug Alcohol Rev.* **2019**, *38*, 781–789, doi:10.1111/dar.12985.
174. Davis, A.K.; Barrett, F.S.; So, S.; Gukasyan, N.; Swift, T.C.; Griffiths, R.R. Development of the Psychological Insight Questionnaire among a Sample of People Who Have Consumed Psilocybin or LSD. *J. Psychopharmacol. (Oxf.)* **2021**, *35*, 437–446, doi:10.1177/0269881120967878.
175. Peill, J.M.; Trinci, K.E.; Kettner, H.; Mertens, L.J.; Roseman, L.; Timmermann, C.; Rosas, F.E.; Lyons, T.; Carhart-Harris, R.L. Validation of the Psychological Insight Scale: A New Scale to Assess Psychological Insight Following a Psychedelic Experience. *J. Psychopharmacol. (Oxf.)* **2022**, *36*, 31–45, doi:10.1177/02698811211066709.
176. Carhart-Harris, R.L.; Bolstridge, M.; Day, C.M.J.; Rucker, J.; Watts, R.; Erritzoe, D.E.; Kaelen, M.; Giribaldi, B.; Bloomfield, M.; Pilling, S.; et al. Psilocybin with Psychological Support for Treatment-Resistant

Depression: Six-Month Follow-Up. *Psychopharmacology (Berl.)* **2018**, *235*, 399–408, doi:10.1007/s00213-017-4771-x.
177. Kähönen, J. Psychedelic Unselfing: Self-Transcendence and Change of Values in Psychedelic Experiences. *Front. Psychol.* **2023**, *14*, doi:10.3389/fpsyg.2023.1104627.
178. van der Tempel, J.; Moodley, R. Spontaneous Mystical Experience among Atheists: Meaning-Making, Psychological Distress, and Wellbeing. *Ment. Health Relig. Cult.* **2020**, *23*, 789–805, doi:10.1080/13674676.2020.1823349.
179. Watts, R.; Day, C.; Krzanowski, J.; Nutt, D.; Carhart-Harris, R. Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression. *J. Humanist. Psychol.* **2017**, *57*, 520–564, doi:10.1177/0022167817709585.
180. Kornfield, J. Intensive Insight Meditation: A Phenomenological Study. *J. Transpers. Psychol.* **1979**, *11*, 41–58.
181. Wolff, M.; Evens, R.; Mertens, L.J.; Koslowski, M.; Betzler, F.; Gründer, G.; Jungaberle, H. Learning to Let Go: A Cognitive-Behavioral Model of How Psychedelic Therapy Promotes Acceptance. *Front. Psychiatry* **2020**, *11*, 5, doi:10.3389/fpsyt.2020.00005.
182. Wolff, M.; Mertens, L.J.; Walter, M.; Enge, S.; Evens, R. The Acceptance/Avoidance-Promoting Experiences Questionnaire (APEQ): A Theory-Based Approach to Psychedelic Drugs' Effects on Psychological Flexibility. *J. Psychopharmacol. (Oxf.)* **2022**, *36*, 387–408, doi:10.1177/02698811211073758.
183. Cordova, J.V. Acceptance in Behavior Therapy: Understanding the Process of Change. *Behav. Anal.* **2001**, *24*, 213–226, doi:10.1007/BF03392032.
184. Malone, T.C.; Mennenga, S.E.; Guss, J.; Podrebarac, S.K.; Owens, L.T.; Bossis, A.P.; Belser, A.B.; Agin-Liebes, G.; Bogenschutz, M.P.; Ross, S. Individual Experiences in Four Cancer Patients Following Psilocybin-Assisted Psychotherapy. *Front. Pharmacol.* **2018**, *9*, doi:10.3389/fphar.2018.00256.
185. Nielson, E.M.; May, D.G.; Forcehimes, A.A.; Bogenschutz, M.P. The Psychedelic Debriefing in Alcohol Dependence Treatment: Illustrating Key Change Phenomena through Qualitative Content Analysis of Clinical Sessions. *Front. Pharmacol.* **2018**, *9*, doi:10.3389/fphar.2018.00132.
186. Soler, J.; Elices, M.; Dominguez-Clavé, E.; Pascual, J.C.; Feilding, A.; Navarro-Gil, M.; García-Campayo, J.; Riba, J. Four Weekly Ayahuasca Sessions Lead to Increases in "Acceptance" Capacities: A Comparison Study With a Standard 8-Week Mindfulness Training Program. *Front. Pharmacol.* **2018**, *9*, doi:10.3389/fphar.2018.00224.
187. Swift, T.C.; Belser, A.B.; Agin-Liebes, G.; Devenot, N.; Terrana, S.; Friedman, H.L.; Guss, J.; Bossis, A.P.; Ross, S. Cancer at the Dinner Table: Experiences of Psilocybin-Assisted Psychotherapy for the Treatment of Cancer-Related Distress. *J. Humanist. Psychol.* **2017**, *57*, 488–519, doi:10.1177/0022167817715966.
188. Healy, C.J. The Acute Effects of Classic Psychedelics on Memory in Humans. *Psychopharmacology (Berl.)* **2021**, *238*, 639–653, doi:10.1007/s00213-020-05756-w.
189. Weiss, B.; Wingert, A.; Erritzoe, D.; Campbell, W.K. Prevalence and Therapeutic Impact of Adverse Life Event Reexperiencing under Ceremonial Ayahuasca. *Sci. Rep.* **2023**, *13*, doi:10.1038/s41598-023-36184-3.
190. Mithoefer, M.C. A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder. Available online: https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/TreatmentManual_MDMAAssistedPsychotherapyVersion+8.1_22+Aug2017.pdf (accessed on 20 July 2024).
191. Ehlers, A.; Clark, D.M. A Cognitive Model of Posttraumatic Stress Disorder. *Behav. Res. Ther.* **2000**, *38*, 319–345, doi:10.1016/S0005-7967(99)00123-0.
192. Hasler, G. Toward the "Helioscope" Hypothesis of Psychedelic Therapy. *Eur. Neuropsychopharmacol.* **2022**, *57*, 118–119, doi:10.1016/j.euroneuro.2022.02.006.
193. Griffiths, R.R.; Hurwitz, E.S.; Davis, A.K.; Johnson, M.W.; Jesse, R. Survey of Subjective "God Encounter Experiences": Comparisons among Naturally Occurring Experiences and Those Occasioned by the Classic Psychedelics Psilocybin, LSD, Ayahuasca, or DMT. *PLOS ONE* **2019**, *14*, doi:10.1371/journal.pone.0214377.
194. Barrett, F.S.; Bradstreet, M.P.; Leoutsakos, J.-M.S.; Johnson, M.W.; Griffiths, R.R. The Challenging Experience Questionnaire: Characterization of Challenging Experiences with Psilocybin Mushrooms. *J. Psychopharmacol. (Oxf.)* **2016**, *30*, 1279–1295, doi:10.1177/0269881116678781.
195. Carbonaro, T.M.; Bradstreet, M.P.; Barrett, F.S.; MacLean, K.A.; Jesse, R.; Johnson, M.W.; Griffiths, R.R. Survey Study of Challenging Experiences after Ingesting Psilocybin Mushrooms: Acute and Enduring Positive and Negative Consequences. *J. Psychopharmacol. (Oxf.)* **2016**, *30*, 1268–1278, doi:10.1177/0269881116662634.
196. Dittrich, A. The Standardized Psychometric Assessment of Altered States of Consciousness (ASCs) in Humans. *Pharmacopsychiatry* **1998**, *31*, 80–84, doi:10.1055/s-2007-979351.
197. Rothbaum, B.O.; Schwartz, A.C. Exposure Therapy for Posttraumatic Stress Disorder. *Am. J. Psychother.* **2002**, *56*, 59–75, doi:10.1176/appi.psychotherapy.2002.56.1.59.
198. Balban, M.Y.; Neri, E.; Kogon, M.M.; Weed, L.; Nouriani, B.; Jo, B.; Holl, G.; Zeitzer, J.M.; Spiegel, D.; Huberman, A.D. Brief Structured Respiration Practices Enhance Mood and Reduce Physiological Arousal. *Cell Rep. Med.* **2023**, *4*, doi:10.1016/j.xcrm.2022.100895.

199. Meuret, A.E.; Ritz, T.; Wilhelm, F.H.; Roth, W.T. Voluntary Hyperventilation in the Treatment of Panic Disorder—Functions of Hyperventilation, Their Implications for Breathing Training, and Recommendations for Standardization. *Clin. Psychol. Rev.* **2005**, *25*, 285–306, doi:10.1016/j.cpr.2005.01.002.
200. Calder, A.; Hasler, G. Extrapharmacological Safety Topics in Psychedelic-Assisted Psychotherapy. *JAMA Psychiatry* **2023**, *80*, 761–762, doi:10.1001/jamapsychiatry.2023.1031.
201. Evans, J.; Robinson, O.C.; Argyri, E.K.; Suseelan, S.; Murphy-Beiner, A.; McAlpine, R.; Luke, D.; Michelle, K.; Prideaux, E. Extended Difficulties Following the Use of Psychedelic Drugs: A Mixed Methods Study. *PLOS ONE* **2023**, *18*, doi:10.1371/journal.pone.0293349.
202. Marrocu, A.; Kettner, H.; Weiss, B.; Zeifman, R.J.; Erritzoe, D.; Carhart-Harris, R.L. Psychiatric Risks for Worsened Mental Health after Psychedelic Use. *J. Psychopharmacol. (Oxf.)* **2024**, *38*, 225–235, doi:10.1177/02698811241232548.
203. Bahi, C.; Irrmischer, M.; Franken, K.; Fejer, G.; Schlenker, A.; Deijen, J.B.; Engelbregt, H. Effects of Conscious Connected Breathing on Cortical Brain Activity, Mood and State of Consciousness in Healthy Adults. *Curr. Psychol.* **2024**, *43*, 10578–10589, doi:10.1007/s12144-023-05119-6.
204. Gellings, T.; Ossebaard, J.; van Schie, H.T. Self-Transcendence in Daily Life and During Meditation in Focused Attention and Open Monitoring Meditators. 2023, *manuscript submitted for publication*.
205. Lalande, L.; Bambling, M.; King, R.; Lowe, R. Breathwork: An Additional Treatment Option for Depression and Anxiety? *J. Contemp. Psychother.* **2012**, *42*, 113–119, doi:10.1007/s10879-011-9180-6.
206. Josipovic, Z. Neural Correlates of Nondual Awareness in Meditation. *Ann. N. Y. Acad. Sci.* **2014**, *1307*, 9–18, doi:10.1111/nyas.12261.
207. Vieten, C.; Wahbeh, H.; Cahn, B.R.; MacLean, K.; Estrada, M.; Mills, P.; Murphy, M.; Shapiro, S.; Radin, D.; Josipovic, Z.; et al. Future Directions in Meditation Research: Recommendations for Expanding the Field of Contemplative Science. *PLOS ONE* **2018**, *13*, doi:10.1371/journal.pone.0205740.
208. Travis, F. Transcendental Experiences during Meditation Practice. *Ann. N. Y. Acad. Sci.* **2014**, *1307*, 1–8, doi:10.1111/nyas.12316.
209. Pérez-Álvarez, M. Psychotherapy as a Human Science, More Than a Technological One. *Papeles Psicólogo - Psychol. Pap.* **2018**, *40*, doi:10.23923/pap.psicol2019.2877.
210. Goodwin, G.M.; Malievskaia, E.; Fonzo, G.A.; Nemeroff, C.B. Must Psilocybin Always "Assist Psychotherapy"? *Am. J. Psychiatry* **2023**, *181*, 20–25, doi:10.1176/appi.ajp.20221043.