Chapter 3
Psychedelic Medicines: A Paradigm Shift from Pharmacological Substitution Towards Transformation-Based Psychiatry

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Psychedelic Medicines Reveal Novel Drug Targets for Mental Health Disorders

Scientific interest into the neurobiology and phenomenology of drug-induced altered states of consciousness and their potential to facilitate therapeutic transformation has resumed. Promising directions include the rediscovery of psychoactive substances for the treatment of various mental health disorders (Nichols, Johnson & Nichols, 2017). During the last decade, the discovery of the antidepressant effect of the dissociative anesthetic ketamine fueled the search for novel drug targets for mood disorders (Murrough, Abdallah & Mathew, 2017). Ketamine was proposed to represent a novel class of rapid-acting glutamatergic antidepressants due to its immediate, albeit transient, antidepressant effect.

Likewise, the therapeutic potential of psilocybin was assessed for various conditions, including end-of-life anxiety, depression, obsessive-compulsive disorder, and nicotine and alcohol addiction, with promising preliminary results (Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Moreno, Wiegand, Taitano & Delgado, 2006). Compared to the transient effects of ketamine, psilocybin showed more sustained improvements in depressive symptoms, even several weeks after a single administration, which continues to inspire the search for rapid-acting serotonergic drug targets.

Recently, due to its therapeutic potential, scientific interest in the N,N-dimethyltryptamine (DMT)-containing Amazonian plant medicine ayahuasca has started to grow (Frecska, Bokor & Winkelman, 2016). In South America, ayahuasca is used in ritualistic settings as traditional medicine for curative and religious purposes by indigenous and mestizo people. Currently, this plant medicine is spreading

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all over the world with increasing numbers of Westerners seeking ayahuasca (Labate & Cavnar, 2014; Labate & Jungaberle, 2011; Tupper, 2008).

This rapid dissemination points (a) to an unmet need for increased psychological wellbeing through rapid and sustainable relief from various mental health problems and (b) to the observational evidence that ayahuasca facilitates transformational processes with beneficial health outcomes. Indeed, ayahuasca users reported greater wellbeing compared to both general psychedelic and nonpsychedelic drug users in a recent global online survey (Lawn et al., 2017).

First evidence from preclinical and human studies suggest that ayahuasca has the potential to reduce symptoms of anxiety and depression (Santos et al., 2016). In an open-label clinical trial in depressed patients, a single dose of ayahuasca showed immediate improvements in depressive symptoms for up to 3 weeks (Osório et al., 2015). Recent data from a randomized controlled trial confirm rapid antidepressant effects of ayahuasca in treatment-resistant patients (Palhano-Fontes et al., 2018, in this volume). However, more systematic research is needed to move beyond observational evidence and further verify therapeutic efficacy and biomechanisms of ayahuasca under controlled conditions.

An Emerging Paradigm Shift from Substitution- to Transformation-Based Therapy

Compared to conventional psychotropic drugs, psychedelic medicines represent a novel class of rapid-acting serotonergic compounds with different mechanisms of action. While ketamine has been mostly used as stand-alone drug treatment with a more biochemically driven mechanism of action, other psychoactive substances such as LSD, MDMA, or psilocybin are preferably studied as adjuncts to psychotherapy, involving an element of guidance, introspection, and self-discovery associated with their positive clinical outcomes. Accordingly, psychedelics administered without psychological support or in less suitable settings without guidance may have limited or even adverse effects. Because psychedelics are increasingly recognized as facilitators of psychotherapeutic processes, rather than just molecular drug targets, it is very likely that we are facing an emerging paradigm shift from pharmacological substitution towards transformation-based psychiatric treatment.

The standard treatment paradigm with pharmaceutical psychotropic drugs is essentially substitution-oriented. Accordingly, mental illness is primarily treated as a disorder caused by certain deficits in brain metabolism, such as neurotransmitter deficiencies of serotonin, norepinephrine, and dopamine that are associated with specific symptoms such as anxious and depressed mood or lack of motivation and energy (Nutt, 2008). Consequently, successful symptomatic treatment includes pharmacological substitution of these neurotransmitter deficits daily, e.g., with an SSRI antidepressant that increases serotonin levels in the brain.

In contrast, the psychedelic-assisted treatment approach as proposed here follows the distinct model of *transformation-based therapy*; psychological illness is not primarily resulting from a deficient brain metabolism that needs to be substituted, but follows from misguided bio-psycho-social processes that await transformation. In contrast to substitution-oriented treatment approaches, the goal of transformation-based therapy is to move the patient from a suboptimal state into a more adaptive state of consciousness that needs to be further stabilized by concurrent psychotherapy. Although maladaptive processes, including stress-related changes in brain chemistry and function, may be associated with deficits in serotonergic or glutamatergic neurotransmission (Popoli, Yan, McEwen, & Sanacora, 2012), these neurotransmitter deficiencies are not necessarily treated as the root cause of psychological suffering. Accordingly, the psychedelic-assisted therapy approach is less based on a long-term pharmacological substitution of neurotransmitters than on a rapid change of dysfunctional neuronal regulatory circuits that allow for a more sustainable process of bio-psycho-social adaptation. The concept of transformation-based therapy, as introduced here, is therefore less focused on the resolution of specific symptoms and their substitution by means of psychotropic drugs, than on empowering the innate dynamic capacity of the patient to regain sustained access to more adaptive states of consciousness that are naturally followed by symptom resolution on many levels.

In clinical settings, psychedelics are hypothesized to work through a biphasic mechanism of action. They act primarily as nonspecific "catalysts" that facilitate the potential for transformative change that has to be specifically guided by psychotherapeutic processes including (1) identification of the dysfunctional states of mental stagnation, (2) setting of conscious intentions towards transformation, (3) providing psychological support during drug-induced altered states of consciousness, followed by (4) posttreatment psychotherapeutic integration to further stabilize adaptive states and prevent relapse into previous dysfunctional states. Secondarily, in the medium and long term, catalytic exposure to psychedelics parallels the effects of adaptogens on the human body and mind. Conceptually, adaptogens are stress response modifiers that nonspecifically increase an organism's resistance to various adverse influences, thereby promoting adaptation to the environment (Panossian, 2017). As outlined below, the psychophysiological effects of ayahuasca are particularly aligned with the adaptogenic activity of specific herbal medicines that exhibit polyvalent beneficial effects on physical and mental health.

Adaptogenic Effects of Ayahuasca on Physical and Mental Health

Current uses of adaptogens in pharmacotherapy are related to their potential for treating stress-related physical, mental, and behavioral disorders. Although the mechanisms of action of adaptogens are specifically related to stress protection and

environmental adaptation, it is very unlikely that the pharmacological activity of phytochemicals is associated with only one specific molecular target. Instead, the metabolic regulation of homeostasis by adaptogens at the cellular and systems levels is associated with a multitude of targets, which requires a holistic network pharmacology approach (Panossian, 2017).

The adaptogenic activity of the ayahuasca brew is predominantly related to its main active ingredients: the psychotropic indole alkaloid N,N-dimethyltryptamine (DMT) and different β-carboline alkaloids (e.g., harmine, harmaline, and tetrahydroharmine). In order for DMT to become bioavailable, oral formulations usually contain plant-based sources of DMT (e.g., from *Psychotria viridis*) combined with β-carbolines (e.g., from *Banisteriopsis caapi*) that act as selective reversible MAO-A inhibitors to prevent degradation of DMT in the body (Callaway et al., 1996). DMT is a structural analogue of serotonin and is widely found in nature, including plants, mammalian organisms, and in human brains and body fluids. DMT interacts with a variety of serotonin receptors, mainly 5HT2A, 5HT2C, and 5HT1A, and also with glutamate, dopamine, acetylcholine, sigma-1, and trace amine-associated receptors (Carbonaro & Gatch, 2016; Valle et al., in this volume).

The widespread changes in neuronal excitability resulting from 5-HT2A receptor activation induce marked psychotropic effects on mood and cognition (Vollenweider & Kometer, 2010). Compared to the rapid onset and experiential intensity of intravenous DMT (Strassman, Qualls, Uhlenhuth & Kellner, 1994), the subjective effects of orally activated DMT in ayahuasca preparations appear in a slower, progressive way and disappear after 4–6 h (Riba et al., 2003), which is much more amenable for psychotherapeutic applications. Similar to other adaptogenic phytochemicals, regular ayahuasca use is considerably safe and does not produce pharmacological tolerance even after repeated administration (Barbosa et al., 2012; Santos et al., 2012).

Traditionally, herbal medicines were used to treat the symptoms of several disorders, which is in line with the broad range of beneficial effects of the β-carboline constituents in ayahuasca and their immunomodulatory, neurotrophic, neuroprotective, cognitive-enhancing, and antidepressant effects, among many others (Moloudizargari, Mikaili, Aghajanshakeri, Asghari, & Shayegh, 2013; Morales-García et al., 2017; Santos & Hallak, 2016). Most notably, recent evidence shows that also DMT is neuroprotective by increasing neuronal cell survival under oxidative stress, suggesting its potential adaptogenic role in counteracting the adverse effects of stress in the body (Szabo et al., 2016). This is of crucial relevance, since stress-related disturbances in brain function are associated with the pathogenesis of many psychiatric disorders. Hence, the pharmacology of ayahuasca is a typical example of the multitarget action of adaptogens and may be particularly well suited for the systemic treatment of complex diseases, chronic conditions, and psychiatric syndromes, where conventional reductionist approaches have often been disappointing.

Adaptogenic Effects of Ayahuasca on Brain Dynamics

Understanding how specific drugs affect the neurodynamics of adaptive and maladaptive behavioral states represents a current research priority in biomedical science. It was recently discovered that resting-state brain activity is organized into multiple large-scale functional connectivity networks that enable efficient neuronal communication between different brain hubs that subserve complex mental functions (Fox, Snyder, Corbetta, Van Essen & Raichle, 2005). Dysfunctional brain network dynamics was found to correlate with symptom severity in various psychiatric conditions, with recovery of connectivity observed following successful treatment (Fox & Greicius, 2010). Hence, psychedelic medicines have been proposed to provide promising tools to enhance therapeutic transformation by resetting the neurocircuits that underlie maladaptive neurobehavioral states (Nichols, Johnson & Nichols, 2017).

The effects produced by classical psychedelics are principally mediated through the serotonergic 5-HT1A/2A receptors (Nichols, 2016). Serotonergic psychedelics, such as psilocybin, LSD, and DMT, share the common biomechanism of increased excitability of the prefrontal cortex via 5HT2A receptor agonism (Vollenweider & Kometer, 2010). Due to widespread changes in neuronal excitability, both short-lived and persisting connectivity networks emerge between brain regions during the psychedelic state that normally do not show significant functional association (Petri et al., 2014; Tagliazucchi, Carhart-Harris, Leech, Nutt & Chialvo, 2014).

Drug-induced increases in global brain connectivity allow for better integration of information, while increased metastability and repertoire of connectivity motives accelerate phase transitions and transformation processes (Gallimore, 2015). The breakdown between conventional pathways of neuronal communication and the formation of novel functional associations is in line with a recent hypothesis that psychedelics lead to entropic activity within the brain (Carhart-Harris et al., 2014). During the drug-induced high entropy state, brain activity is less constrained and allows for a larger repertoire of states that succeed in a more random fashion.

The observed increase in entropy may be related to the temporary removal of some of the restrictions that are necessary for sustaining ordinary consciousness resulting in a more flexible mental state. Consistent with this hypothesis, increased brain entropy and changes in global network integration were found subsequent to ayahuasca ingestion (Viol, Palhano-Fontes, Onias, Araujo & Viswanathan, 2017). Phenomenologically, this slightly higher entropy state is perceived as experientially richer, but not as informative as normal waking consciousness: The way meaning is attributed to things is broadened, expanding the sense of reality, including experiential novelty or even bizarreness. This higher entropy state is associated with increased cognitive flexibility, creativity, and imagination (Gallimore, 2015). From a therapeutic perspective, such broadband alterations in functional network connectivity may increase global brain plasticity, whereby the maladaptive patterns that are linked to dysfunctional emotions, thought patterns, and behaviors can be transformed.

Depressive symptomatology is thought to arise from a distorted sense of self, one's relation to others, and the external world, as reflected in disrupted brain connectivity in self-referential information processing networks (Nejad, Fossati & Lemogne, 2013). If depression is redefined as the tendency to enter into, and the inability to disengage from, a negative mood state, rather than the mood state per se (Holtzheimer & Mayberg, 2011), then targeting maladaptive forms of rumination and their underlying neural correlates may become key for effective treatment. Accordingly, active pharmacological disruption of pathological connectivity in core networks relevant to depression would be expected to mediate adaptive changes in brain network dynamics within the plasticity window that opens after drug administration.

Recently, the default mode network (DMN) was proposed as a target for such network-based interventions, because it shows pathological hyperactivity and connectivity in depression and is linked to maladaptive patterns of ruminative self-referential information processing (Sheline, Price, Yan & Mintun, 2010). Interestingly, rapid-acting glutamatergic antidepressants such as ketamine were found to decrease connectivity within key brain networks such as the DMN (Lehmann et al., 2016; Scheidegger et al., 2012). A similar pattern of attenuated DMN activity or connectivity was found for serotonergic drugs such as psilocybin (Carhart-Harris et al., 2012), ayahuasca (Palhano-Fontes et al., 2015; Valle et al., in this volume), and following successful antidepressant treatment (Nejad, Fossati & Lemogne, 2013). This supports the notion that rapid antidepressant action relies on attenuation of self-referential information processing systems such as the DMN. In conclusion, these findings suggest that the pharmacological modulation of glutamate- and serotonin-responsive cerebral circuits that are associated with a disruption of the habitual brain network architecture and an overall increase in brain entropy, represent early biomechanisms to break out of the inflexible and self-referential modes of thinking that characterize depression.

Adaptogenic Effects of Ayahuasca on Mental Functioning

Besides the biological effects, there is a wide range of drug-induced psychedelic experiences that are valued as personally meaningful and deeply transformative. The psychotropic effects of ayahuasca typically include a heightened state of introspection characterized by increased awareness, dreamlike visions and geometric patterns, evocation of intense emotions, and recollection of autobiographical memories. Occasionally, ayahuasca visions also include archetypal or psycho-spiritual themes (Shanon, 2002). Accordingly, cerebral areas associated with episodic memories, internal sensations, and conscious experience of emotions were found to be activated following ayahuasca intake (Riba et al., 2006; Valle et al., in this volume), thereby allowing for improved cognitive-emotional integration.

Insight into maladaptive behavioral, emotional, and cognitive patterns reflects the general action of ayahuasca as a psycho-integrative medicine: brain activity that

is normally driven by prefrontal cognitive control mechanisms is shifted towards intense emotionally laden discharges from the lower limbic areas of the brain (Frecska, Bokor & Winkelman, 2016). Contrary to other psychotropic drugs such as opioids, benzodiazepines, or antipsychotics that tend to cloud and narrow the field of consciousness, ayahuasca usually increases the level of mental clarity and emotional awareness compared to everyday consciousness. Thus, dysfunctional thoughts and emotions can be better recognized, restructured, and integrated, which accelerates and deepens the process of psychotherapeutic transformation. This may benefit patients suffering from unresolved emotional traumas and conflicts that await conscious resolution and reframing.

Many psychiatric symptoms result from early childhood trauma and attachment disorders, which limit the ability to relate and increase vulnerability due to lower stress resilience and reduced interpersonal coping strategies. Since early traumas affect the preverbal phases of human development, they are often difficult to resolve through cognitive-behavioral therapy, which is more palliative by providing basic skills to alleviate symptoms. For patients suffering from emotional neglect and attachment disorders, psychedelic-assisted therapy could resolve interpersonal deficits in more profound and sustainable ways. In supportive environments, psychedelics promote feelings of trust, empathy, bonding, closeness, tenderness, forgiveness, acceptance, and connectedness (Belser et al., 2017; Watts Day, Krzanowski, Nutt & Carhart-Harris, 2017). These empathogenic effects can serve in developing increased levels of relational embeddedness, self-acceptance, and self-care through direct experience of corrective emotions. With increased levels of connectedness to the self, to others, and to the environment (Carhart-Harris, Erritzoe, Haijen, Kaelen & Watts, 2017; Forstmann & Sagioglou, 2017), self-destructive behavioral patterns can be attenuated and general improvement in relationship homeostasis may be reached. This facilitates posttraumatic growth by contributing to the resolution of behavioral consequences of traumas by releasing the person from dysfunctional habits that underlie the dynamics of self-destructive and addictive behaviors (Argento, Capler, Thomas, Lucas & Tupper, in this volume). Indeed, a recent observational study highlights the therapeutic value of ayahuasca in reducing eating disorder symptoms by experiencing greater self-acceptance, increased capacity to regulate painful emotions, and gaining insights about the root causes of the illness (Lafrance et al., 2017; in this volume). Through enhanced awareness of the likely personal consequences of maladaptive behaviors, ayahuasca may provide a motivation for more sustained changes in attitudes and behaviors.

Another way of understanding psychedelic-assisted transformation is to compare it with the behavioral technique of exposure therapy: Anxiety is usually best resolved through repeated exposure to the feared object or context. Comparably, psychedelic experiences share the same sequence of exposing the patient to the entire possible spectrum of intense feelings and mental states. Ayahuasca experiences are often described as going through an initial state of confronting innermost fears: fear of insanity, fear of death, paranoid thoughts, or the despair of loneliness and rejection (Kjellgren, Eriksson & Norlander, 2009). If the subject is able to surrender, this challenging initial phase is usually followed by a sudden transformation

of the experience into emotional relief, insightful reflections, states of self-transcendence, and changed worldview and outlook on life (Frecska, Bokor, & Winkelman, 2016). In analogy to behavioral exposure therapy that aims at decreasing fear responses, a state of nonspecific stress resistance could be achieved by adaptogens such as ayahuasca. Through repeated exposures to the psychedelic state, the mind trains its intrinsic capability to deal with difficult emotions that may finally lead to a more relaxed and accepting attitude towards general human suffering. Indeed, a recent observational study of people suffering from the death of a loved one found lower levels of grief in ayahuasca users, suggesting its potential to increase the capacity to deal with difficult emotions (González, Carvalho, Cantillo, Aixalá & Farré, 2017).

From a psychological perspective, enhanced cognitive flexibility, creativity, and imagination are generally found in psychedelic states, with long-term increases in creative problem-solving abilities and the personality trait of openness (Lebedev et al., 2016; Maclean, Johnson & Griffiths, 2011; Sweat, Bates & Hendricks, 2016). The adaptogenic potential of ayahuasca might therefore be specifically related to its ability to increase cognitive flexibility, e.g., through divergent thinking (Kuypers et al., 2016; Mason and Kuypers, in this volume). Ayahuasca was also found to elevate levels of mindfulness, self-compassion, and "decentering," which refers to the capacity to observe thoughts and emotions as transitory mental events without being trapped by them (Sampedro et al., 2017; Soler et al., 2016; Valle et al., in this volume). Changes in cognitive flexibility and mindfulness-related capabilities strongly support the implementation of concomitant psychotherapy to train patients how to stabilize and maintain more balanced states of mind that allow for a better adaptation to their environment. Indeed, longitudinal observational studies reported that ayahuasca users are well adapted and integrated in their social, working, and familiar environments and that ayahuasca is used as a tool for personal development (Bouso et al., 2012).

Converging Roles of Mindfulness and Psychedelics for Transformational Mental Healthcare

From a phenomenological perspective, some drug-induced peak experiences share a striking resemblance to mystical experiences reached in deep meditation. In these states, the usual ego boundaries are dissolved to a degree where the subject of experience feels universally connected with all existence. Such transformative experiences can be achieved by various consciousness-altering techniques, such as artistic creativity, ecstasy, psychedelics, trance, meditation, and relaxation.

In his cartography of ecstatic and meditative states (see Fig. 3.1), Roland Fischer considered the varieties of human experience on (1) the perception-hallucination continuum of increasing *ergotropic arousal* (e.g., creative, psychotropic, and ecstatic experiences) and (2) along the perception-meditation continuum of

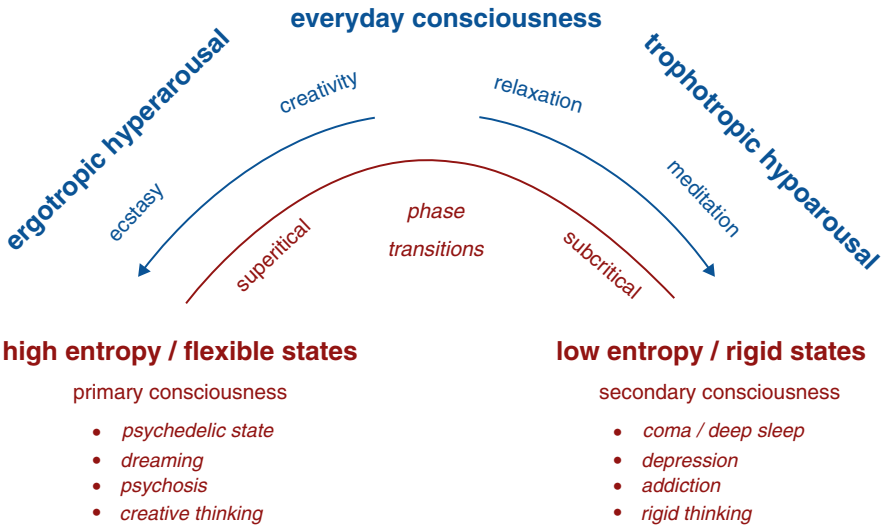

Fig. 3.1 Phenomenological map of altered states of consciousness. A continuum of ergotropic vs. trophotropic arousal (top spectrum; adapted from Fischer, 1971) is contrasted with high entropy primary consciousness vs. low entropy secondary consciousness (bottom spectrum; adapted from Carhart-Harris et al., 2014)

increasing *trophotropic arousal* (e.g., hypo-aroused meditative states) (Fischer, 1971). Both directions represent changes in self-referential processing in terms of mutually exclusive psychophysiological alterations of everyday consciousness. While the creative person or meditation expert has learned to purposefully navigate through different states of consciousness, mental illness is characterized as the loss of freedom to skillfully navigate towards more adaptive mental states.

With progression towards peak or breakthrough states of ego dissolution and self-transcendence, therapeutic transformation, or "unlearning" of previously conditioned self-referential behaviors and attitudes, is facilitated. But, due to their mutually exclusive psychophysiology, ordinary and altered states of consciousness cannot occur at the same time, which raises questions of transfer and stabilization: How can brief transformative moments of altered perception be integrated within the boundaries of everyday consciousness? To further develop and maintain mindfulness-related capabilities, sustainable therapeutic transformation strongly relies on concomitant mental training, otherwise short-term beneficial effects are likely to fade away.

Fischer's two-sided phenomenological map of altered states of consciousness parallels contemporary adoptions of Freudian ideas into the entropic brain hypothesis (Carhart-Harris et al., 2014). Freud divided the psyche into two fundamentally distinct modes of activity: the primary process and the secondary process (Freud, 1995). Dreaming and psychosis typify a primitive style of thinking, directly animated by the drives, that is dominant in infancy and characterized by disorder, conceptual paradox, symbolic imagery, intense emotions, and animistic thinking. The

entropic brain hypothesis refers to this mode of cognition as "primary consciousness," which is characterized by unconstrained thinking and less ordered higher brain entropy dynamics.

Healthy psychological life results from an adaptive equilibrium between *primary* and s*econdary processes*, which presuppose the binding of free-flowing energy, by intervening as a system of control characterized by order, precision, conceptual consistency, controlled emotions, and rational thinking. This constrained style of cognition is dominant in normal waking consciousness, referred to as "secondary consciousness," which is associated with more ordered neurodynamics.

Following this model, the phenomenology of psychedelic states is characterized by phase transitions from more rigid and inflexible secondary states towards less-constrained primary states characterized by elevated levels of brain entropy and uncertainty, corresponding to the ergotropic spectrum of consciousness (see Fig. 3.1). This psychedelic-induced regression into primary consciousness through temporarily relaxed neurophysiological constraints explains psychedelic phenomena such as expanded perception, vivid imagination, emotional intensity, conceptual paradox, and loss of usual self-boundaries.

Interestingly, drug-induced altered states (e.g., ketamine, psilocybin or ayahuasca) share very similar neuronal biosignatures as altered states reached by non-pharmacological methods (e.g., meditation): The expanded state of consciousness is generally associated with reduced activity or connectivity in cortical midline areas that mediate self-referential information processing, such as the default mode network (DMN) (Brewer et al., 2011; Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015; Scheidegger et al., 2012). Such states of attenuated self-referential processing are of particular clinical importance. While the field of consciousness is usually narrowed in depressive, anxious, obsessive-compulsive, or addictive states, it can be broadened towards more flexible and less biased modes of conscious awareness as a result of psychedelic-assisted therapy. Negative emotional biases related to critical self-referential processing are particularly well-resolved through mindfulness training that develops skills such as meta-awareness, self-regulation, and a positive relationship between self and other that transcends self-focused needs and increases pro-social characteristics (Vago & Silbersweig, 2012). Likewise, improvements in mindfulness-related capabilities may be enhanced not only by meditation practices but also through distinctive features of transformative experiences induced by ayahuasca or psilocybin (Griffiths et al., 2017; Soler et al., 2016).

In settings that are supportive for cultivating mindfulness, drug-induced mystical-type experiences facilitate enduring trait-level increases in pro-social attitudes and behaviors such as interpersonal closeness, gratefulness, forgiveness, and purposefulness, thereby supporting psycho-spiritual development (Griffiths et al., 2017). Most notably, the intensity of drug-induced mystical-type experiences was found to be predictive of positive long-term outcomes in several clinical studies (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014; Griffiths et al., 2016; Roseman et al., 2018; Ross et al., 2016). Through expanded states of consciousness, patients may become increasingly aware of how to navigate their own consciousness and break out from maladaptive states through increased meta-awareness and cognitive flexibility. The

induction of transformative experiences and mindfulness-related capabilities is therefore expected to contribute to the noted increases in wellbeing and mood following exposure to psychedelics.

From a conceptual perspective, it makes sense to assume that through attenuation of ego boundaries and expansion of consciousness towards states of self-transcendence, a transient state of release from clinical symptoms is induced. This follows logically from the notion that symptoms arise at the interface between the individual and its environment, signaling a homeostatic imbalance with a need for behavioral adjustment or removal of noxious influences. When ego boundaries are dissolved to a degree where the conceptual distinction between external and internal world is suspended, there is no interface for the generation of symptoms anymore. With progressive reorientation in body, space, and time, the constructivist and process-related dynamics of symptom formation and possible avenues for their resolution become more evident to the patient. From this clinical epistemological perspective, it can be argued that drug-induced states of self-transcendence provide unique chances to gain metacognitive awareness into the intrinsic dynamic of root causes and processes underlying the formation of symptoms and open a psychotherapeutic window for adaptation, transformation, and personal growth.

Transformational Psychotherapy as an Emerging New Treatment Paradigm

The transformation-based psychotherapy framework, as proposed here, is very aligned with process-oriented adaptations of third wave cognitive behavioral therapies (CBT). While standard CBT is more outcome-oriented, modifying psychiatric symptoms as directly as possible, the third wave of CBT emphasizes a set of new behavioral and cognitive approaches such as emotions, relationships, values, mindfulness, acceptance, and meta-cognition. Established therapeutic approaches include acceptance and commitment therapy (ACT), dialectical behavior therapy (DBT), mindfulness-based cognitive therapy (MBCT), meta-cognitive therapy (MCT), compassion-focused therapy (CFT), and many others (Hayes & Hofmann, 2017). As reviewed above, the adaptogenic effects of ayahuasca on psychological functioning are particularly aligned with mindfulness-based approaches (Soler et al., 2016; Valle et al., in this volume), that aim to increase acceptance, self-compassion, present-moment and meta-cognitive awareness, and psychological flexibility in the service of achieving core life values (Hayes, Levin, Plumb-Vilardaga, Villatte & Pistorello, 2013).

Adaptive changes in value orientation are likely to follow from recognition of maladaptive orientations (e.g., self-centeredness, addictive cravings, experiential avoidance). Accordingly, a process-oriented view on therapeutic transformation is encouraged, starting with the assessment of the current state of stagnation and identifying the direction for adaptive change by encouraging an awareness of the patient's potential for self-direction. Ayahuasca may become particularly useful to

support this process of self-discovery, creation of meaning, and enriching the patient's self-awareness towards the attainment of insight, sense of agency, identity, self-esteem, emotional awareness, and increased psychological wellbeing.

Although psychedelic medicines show considerable promise as tools for psychotherapeutic transformation, they also pose considerable challenges on currently established treatment paradigms. In the case of depression, a significant number of patients treated according to the substitution-based approach with an SSRI antidepressant fail to respond adequately (Gaynes, 2009) or relapse shortly after initial therapeutic progress. Are these the patients that might benefit from psychedelic-assisted therapy instead?

Possible answers are provided by the bipartite model of brain serotonin function that was proposed recently to contrast different therapeutic approaches to emotional processing (Carhart-Harris & Nutt, 2017). The chronic antidepressant action of SSRIs reduces limbic responsiveness and increases emotional resilience to environmental stress, likely via postsynaptic 5-HT1A receptor signaling. This contrasts with the more important role of 5-HT2A receptor signaling for psychedelics, which promotes emotional release and active coping, and requires willingness of the patient to confront and work through sources of stress during the window of plasticity opening after drug administration.

Psychedelic-assisted therapy might therefore be particularly well suited for patients with so-called psychoneurotic disorders to loosen otherwise fixed maladaptive patterns of cognition and behavior so they might overcome symptoms that are usually more challenging to resolve within the substitution-oriented paradigm. But what about the treatment-resistant patients with more serious psychiatric illnesses or complex traumatic histories, personality disorders, and other comorbidities? The clinical decision whether a patient is better cared for in a palliative or substitution-oriented framework or whether he might benefit from psychedelic-assisted transformational psychotherapy necessitates a careful medical screening, indication, and risk-benefit analysis, which requires a high level of clinical expertise.

Another limiting factor is that pretreatment with serotonergic antidepressants attenuates the effects of serotonergic psychedelics due to altered 5HT2A-receptor function, therefore substitution- and transformation-based approaches cannot be combined at the same time (Bonson, Buckholtz & Murphy, 1996). Hence, if psychedelic-assisted therapy is becoming an established treatment approach in the near future, strategies to stratify patient populations to substitution- versus transformation-based treatments become crucial to ensure clinical benefit and safety.

The Ritual Use of Psychedelic Medicines in Nonclinical Settings

The effects of psychedelic medicines as nonspecific amplifiers of subjective experience are highly context-dependent. In nonclinical indigenous or psychospiritual settings, altered states of consciousness are traditionally experienced in group rituals or ceremonies. The ritual itself facilitates transitions between different states of

consciousness through heightening levels of awareness, synchronizing bio-psycho-social rhythms, and shifting mental processes towards more creative-imaginative and emotional directions.

During the process of loosening of ego boundaries, the ritual provides a safe space for the loss of conscious control. When a group of individuals moves from a solid self-centered to a more liquid state of group dynamics, individuals sometimes feel like merging into a coherent group organism, accompanied by a sense of solidarity and transcendence that is perceived as deeply joyful, cathartic, purposeful, or even spiritual (Kent, 2010). Through setting predefined personal intentions before the ritual, an attitude of positive expectancy for individual or collective transformation is generated and supports the broadening of conscious perspectives from the habitual towards the realm of new possibilities.

Besides encouraging insight, meaning, compassion, and connectedness, rituals can also provoke challenging cathartic experiences, strengthening acceptance of unpleasant feelings, loss of control, and general human suffering. Hereby the whole spectrum of experiences that are part of human existence, including states of ego dissolution and self-transcendence, are safely contained within ritual practices that encourage the opportunity for mutual social support and emotional bonding among participants, motivating lasting behavioral changes. Further anthropological and ethnographical investigations about the traditional ritualistic use of psychedelic medicines (Labate & Cavnar, 2014; Labate Cavnar & Gearin, 2016) and the importance of contextual factors could be informative to design prospective therapeutic environments.

Future Directions and Challenges

The challenge of how a traditional indigenous practice can be translated into the Western world remains. Taking a pragmatic stance might be useful to resolve the tensions between different belief systems that naturally create separation and dissent. If the commonly valued goal of medicinal use of ayahuasca is to reduce human suffering, then it seems legitimate to introduce a traditional Amazonian plant medicine into contemporary clinical practice if there is evidence-based proof for its therapeutic efficacy.

A pragmatic knowledge transfer does not necessarily require adopting the entire ceremonial context with an indigenous shaman and associated spiritual belief systems for the medicine to work properly. Pragmatism primarily motivates a careful analysis of the functional role of the medicine in a given context. What is the functional role of ayahuasca in the traditional indigenous context? How is therapeutic transformation facilitated, and what are the necessary conditions to secure participants safety and beneficial outcomes? The same pragmatic questions apply to other contexts: How does ayahuasca work in a way that makes sense to the Western mind? What are the essential functional conditions that need to be met to achieve a desired therapeutic outcome? How should the traditional setting be adapted and which

belief systems do we create to make sense of the ayahuasca experience? The answers might look very different depending on context, because pragmatism is not oriented towards finding absolute truths, but is more focused on revealing what works best in a given context. While traditionalists might emphasize the need for strict rules and orthodoxy to preserve a specific tradition that evolved around the ingestion of ayahuasca, I am advocating here for the possibility of change and cultural evolution. If we allow different cultures and approaches to merge, there is true chance for discovery and innovation by means of pragmatic knowledge transfer.

The same reasoning applies to questions about whether it is necessary to work with the whole molecular plant matrix that is contained in the original ayahuasca plant species, or if a scientific version of "pharmahuasca" will have similar experiential and therapeutic properties, if only a limited number of active ingredients is extracted and standardized according to the protocols of pharmaceutical science and tested under empirically controlled laboratory conditions.

If science and medicine are ready to adopt ayahuasca into their pharmacopoeia of approved medicinal herbs, the future will teach us how pharmahuasca may become an evidence-based treatment for various mental health problems, and how the indigenous wisdom that evolved around the traditional use of ayahuasca may contribute to meet the challenges of intercultural knowledge transfer.

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