Phenomenology, Structure, and Dynamic of Psychedelic States

Katrin H. Preller and Franz X. Vollenweider

Abstract Classic serotonergic hallucinogens or psychedelics produce an altered states of consciousness (ASC) that is characterized by profound alterations in sensory perception, mood, thought including the perception of reality, and the sense of self. Over the past years, there has been considerable progress in the search for invariant and common features of psychedelic states. In the first part of this review, we outline contemporary approaches to characterize the structure of ASCs by means of three primary etiology-independent dimensions including oceanic boundlessness, anxious ego-dissolution, and visionary restructuralization as well as by 11 lower-order factors, all of which can be reliably measured by the altered state of consciousness questionnaire (APZ-OAV). The second part sheds light on the dynamic nature of psychedelic experiences. Frequently, psychedelic subjects progress through different stages over time and levels of changes along a perception-hallucination continuum of increasing arousal and ego-dissolution. We then review in detail the acute effects of psychedelics on sensory perception, emotion, cognition, creativity, and time perception along with possible neural mechanisms underlying them. The next part of this review outlines the influence of non-pharmacological factors (predictors) on the acute psychedelic experience, such as demographics, genetics, personality, mood, and setting, and also discusses some long-term effects succeeding the acute experience. The last part presents some recent concepts and models attempting to understand different facets of psychedelic states of consciousness from a neuroscientific perspective.

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Keywords Psilocybin · Lysergic acid diethylamide (LSD) · Hallucinogens · Psychedelics · Altered states of consciousness · Serotonin · Human

Contents

1 Introduction

Classic hallucinogens or psychedelics such as LSD, psilocybin, DMT, and mescaline comprise a group of compounds all of which produce a so-called altered state of consciousness (ASC) that is characterized by profound alterations of sensory perception, mood, thought, perception of reality, and the sense of self (Hofmann 1968). All of these classic hallucinogens are agonists or partial agonists at serotonin 5-HT2 receptors; additionally, the tryptamines activate 5-HT1, 5-HT6, and 5-HT7 receptors, whereas LSD also directly stimulates dopamine D1 and D2 receptors (Nichols 2004). Substantial evidence demonstrates that activation of 5-HT2A receptors by classic hallucinogens is a primary key mechanism to psychedelic symptom formation in humans (Vollenweider 1998; Vollenweider et al. 1998). Since the 1990s, there has been a growing interest in the investigation of the complex phenomenology and neuronal correlates of hallucinogen-induced ASCs in humans, facilitated by recent advances in concepts and techniques in cognitive neurosciences (Geyer and Vollenweider 2008; Vollenweider 1998; Vollenweider and Geyer 2001; Vollenweider and Kometer 2010).

The study of hallucinogens in humans is important for several reasons, as follows. First, hallucinogens affect a number of psychological domains and brain functions, including emotional and social behaviors, cognitive-thoughtful functions, and self-awareness, that typically characterize the human mind and cannot be reliably studied in behavioral animal models (Hanks and Gonzalez-Maeso 2013). Second, hallucinogens can elicit a clinical syndrome that in several aspects resembles the incipient stages of the spectrum of schizophrenic psychoses or the acute stages of mania-like disorders (Geyer and Vollenweider 2008; Gouzoulis-Mayfrank et al. 1998a; Vollenweider 1998; Vollenweider et al. 1998). Third, there is accumulating evidence that hallucinogens have clinically relevant effects as adjuncts in the treatment of depression, anxiety, obsessive–compulsive disorder, and addictions (Bogenschutz et al. 2015; Grob et al. 2011; Leuner et al. 1994; Moreno and Delgado 1997). Finally, hallucinogens represent a unique heuristic experimental tool that can provide novel insights into the dimensions of the human unconscious and the basis for creativity (Masters and Houston 2000; Sessa 2008).

Over the years, several attempts have been made to find a universally accepted taxonomy to describe the different facets of the phenomenology produced by classic hallucinogens (Leuner 1981; Schultes and Hofmann 1980). At the present time, the term *hallucinogen* is the most common designator in the scientific literature, although it is somewhat of a misnomer because true hallucinations rarely occur at low-to-medium doses. *Hallucinogen* is often used interchangeably with the term "psychotomimetic" (psychosis-mimicking), which emphasizes the psychosis-like symptoms induced by these agents. More recently, the more popular term "psychedelic," meaning mind-manifesting, has also been employed in scientific publications; *psychedelic* was coined to convey the fact that the psychological state induced by hallucinogens is not defined by pathological features but rather by a general activation and manifestation of the experiential and behavioral repertoire of the psyche (Osmond 1957).

By the late 1970s, more than 1000 papers had been published describing the psychological, behavioral, or clinical effects of classic hallucinogens in normal subjects or in psychiatric patients. Several attempts were made—using a plethora of approaches—to describe and categorize the wide range of phenomena occurring during psychedelic states. The methods and instruments used to describe the acute phenomenology of psychedelic states ranged from narrative reports and subjective first-person accounts to a variety of psychological, cognitive, behavioral, and psychopathological measures, but also included process-related constructs and terms borrowed from psychoanalytical theories, as well as Gestalt and transpersonal psychology. The various approaches used to probe the topography and dynamics of the psychedelic experience are well documented in three comprehensive monographs (Grof 1975; Leuner 1962; Masters and Houston 2000). For example, Master and Houston (2000) suggested that the psychological features and processes characterizing psychedelic states in healthy subjects fall into four broad categories: changes occurring at the sensory level, at the recollective–psychodynamic level, at the affective and symbolic level, and at the deep integral level of self-transcendence. Similar experiential categories and comparable processes were described by Grof (1975) in psychiatric patients undergoing psychedelic-assisted psychotherapy.

Although these early categorization attempts provided important insight into the content and dynamics of the psychedelic experience, an accurate detection of patterns in the features of the psychedelic experience remained problematic. The identification of structural features was hampered by the fact that the theoretical framework and methods used differed markedly across studies and that some of the proposed categories denote the method used to get to a particular state rather than the experiential state itself. Moreover, personal narratives, unvalidated self-report measures, and clinical descriptions may be well suitable to extract a lower-order classification of psychedelic states, but they are not sufficient to detect a higher-order structure, e.g., orthogonal dimensions of psychedelic experiences.

To overcome some of these methodological problems, Dittrich and his co-workers (Dittrich 1985, 1998; Dittrich et al. 1981, 1985) conducted a series of studies to empirically test the hypothesis that pharmacological and non-pharmacological-induced ASCs share certain core dimensions, independent of the method of induction or intensity (Ludwig 1966). This initial work and subsequent validation studies yielded a 3-factorial structure of ASCs and led to the development of the altered state of consciousness questionnaire (APZ) (Dittrich 1985), as well as its revised versions, the APZ-OAV (Dittrich 1998) and the 5D-ASC (for a review, see Studerus et al. 2010). The 5D-ASC comprises three primary etiology-independent dimensions: oceanic boundlessness (OBN), anxious ego-dissolution (AED), and visionary restructuralization (VIR), as well as two secondary dimensions: acoustic alterations (AA) and vigilance reduction (VR); these five dimensions measure characteristic patterns of changes ranging from sensations to self-awareness. Dittrich had theorized that detection of such invariant core dimensions of ASCs may lead to a more coherent taxonomy of ASCs and may facilitate the identification of neuronal correlates of the different facets of the subjective experiences in ASCs. More recently, using a large dataset, Studerus et al. (2010) demonstrated that ASCs can be described by 11 lower-order factors that are highly measurement invariant across various drug conditions and settings. Two other instruments that are used to measure the subjective experience of ASCs in current hallucinogen research are the Phenomenology of Consciousness Inventory (Pekala et al. 1986) and the Hallucinogen Rating Scale (HRS), which was developed by Strassman et al. (1994) and later validated by Riba et al. (2001).

Since the 1990s, the APZ questionnaires has been included in more than 80 studies to assess the psychological effects of different classes of psychoactive drugs including psilocybin, ketamine, DMT, and mescaline and to link first-person accounts to various cognitive, behavioral, and neurophysiological measures of ASCs including positron emission tomography (PET), electroencephalography (EEG-ERP), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI). Several studies focused on the pharmacokinetics, metabolism, and receptor profile of psilocybin and its relationship to the various facets of the psychedelic experience, while other studies have explored the dose-response, tolerability, and side effects of psilocybin in healthy subjects. Moreover, some early studies using psychophysiological approaches explored the relationship between specific subjective symptoms (e.g., the sensation of a color) and objective physical

measures (e.g., a change in brightness) induced by psilocybin and LSD in healthy subjects (for review see Fischer 1971). Many of the recent studies used psilocybin or DMT within the model psychosis framework as tools to identify the neuronal underpinnings of psychotic symptom formation, including hallucinations, thought disorder, and disturbances of the self (Geyer and Vollenweider 2008). For instance, some studies tested the hypothesis that deficits of basic information processing functions (such as sensory gating and perceptual learning) contribute to the generation of psychosis-like symptoms and cognitive alterations in psychedelic states. Other studies have specifically focused on the neural basis of perceptual alterations such as the sense of time, binocular rivalry, and hallucinations. More recent work has also re-investigated the potential for psilocybin to induce a positively experienced self-dissolution as a central feature of so-called mystical experiences and its ability to produce long-lasting positive changes in attitude, mood, and behavior in healthy subjects (Griffiths et al. 2006).

The present review is concerned with the phenomenology of psychedelic states and particular with characterization of the effects of classic hallucinogens on perception, emotion, cognition, and the sense of self in healthy subjects. Given that most of the recent studies were conducted with psilocybin, and because the psychological peak effects of psilocybin could not be distinguished from those of LSD or mescaline in controlled studies, we will focus on recent and early studies that attempted to identify neuronal correlates of psychedelic features induced by psilocybin. Furthermore, we attempt to characterize psilocybin-induced states by content, structure, and distinct stages of a psilocybin-induced dynamic process and will discuss some conceptual issues and difficulties encountered.

2 Structure and Basic Dimensions of Psychedelic Experiences

The term “altered state of consciousness” (ASC), coined by Ludwig in (1966), refers to a mental state that is induced by physiological, psychological, or pharmacological manipulations and significantly deviates from normal waking consciousness (Ludwig 1966). Following Moreau De Tours (1973), Ludwig formulated the hypothesis that deliberately and disease-induced ASCs share common core dimensions. Ludwig’s hypothesis was empirically tested and validated by Dittrich (1985) in a series of studies using various ASC-inducing methods (e.g., hallucinogens, hypnosis, and sensory overload). This work revealed that the structure of ASCs comprises three primary etiology-independent dimensions: oceanic boundlessness (OBN), anxious ego-dissolution (AED), and visionary restructuralization (VIR), which can be reliably measured by the APZ-OAV altered state of consciousness questionnaire (Dittrich 1985, 1998).

The OBN dimension reflects a highly pleasurable state of self-dissolution and comprises items that measure alterations of ego-boundaries, an experience of unity and transcendence of space and time, spiritual experiences, a sense of intuitive

understanding, and changes in emotions ranging from heightened mood to bliss and ecstasy. The items in the OBN dimension can be categorized into five item-groups: depersonalization and derealization, changes in the sense of time, positive mood, and mania-like symptoms (see Fig. 3). Given that many of the OBN items have been based on six of the nine core characteristics of so-called "mystical" experiences defined by Stace (1961), high OBN scores may be indicative of mystical experiences, as described in the scientific literature on the psychology of religion (Forman 1990).

The AED dimension denotes a state of anxious ego-dissolution that is characterized by disintegration of the coherent self/ego or separation of the self from the world, loss of self control over one's autonomy, feelings of estrangement from the environment, cognitive impairment, anxiety or panic, and motor disturbances or catatonia. The respective item-groups assess negatively experienced derealization, thought disorder, paranoia, loss of thought control, and loss of body control. High AED scores can reflect a highly unpleasant state that is often referred to colloquially and in the literature as "bad trip." The disruption of the ego as a fundamental unifying drive for integration, organization, and meaning, and impairment of differentiation between ego and non-ego spheres, are highly reminiscent of the acute stages of schizophrenic decompensations (for review see Chapter—Krähenmann, Hermle).

The VIR dimension comprises items assessing elementary and complex pseudohallucinations or true hallucinations, illusions, audio-visual synesthesias, changed meaning of percepts, vivid recollection of memories and imagery from memory, and facilitated imagination. Together, these perceptual phenomena may represent what has been described as hallucinatory visions or "visionary experiences" by religious and historical figures such as Theresa von Avila, Plotin, Eckhart or Shankara (Forman 1990).

However, Dittrich's original work and subsequent investigations suggested that two additional—although etiology-dependent—dimensions exist: **acoustic alterations** (AA), relating to distortions, illusions, and hallucinations in the acoustic sphere, and **vigilance reduction** (VR), which depicts dreaminess, reduced alertness, and drowsiness (Dittrich 1998; Studerus et al. 2010). These additional dimensions were included in the five dimensions of altered states of consciousness (5D-ASC), a revised version of the APZ-OAV questionnaire.

Although the three original OBN (O), AED (A), and VRS (V) dimensions were believed to be factorially invariant across ASC induction methods (Dittrich 1998), a recent re-examination of the APZ-OAV structure using pooled data from 43 controlled studies conducted with psilocybin, (*S*)-ketamine, and MDMA was only able to partially confirm this assumption. Using advanced statistical methods, Studerus and co-workers found that the primary APZ-OAV scales are multidimensional and the VRS dimension can be merged with the OBN dimension at the highest level of construct hierarchy (Studerus et al. 2010). Moreover, Studerus and co-workers were able to extract 11 new homogenous lower-order factors (subscales), which are highly measurement invariant across drug condition, setting, and gender (Studerus et al. 2010). The subscales were termed as follows: experience of unity, spiritual

experiences, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, elementary imagery, complex imagery, audio-visual synesthesiae, and changed meaning of percepts (Fig. 1).

These new subscales have recently been used to compare the subjective effects of psilocybin with those of (*S*)-ketamine and MDMA in healthy subjects. As shown in Fig. 2, despite some similarities, the profile of the subjective effects of classic hallucinogens can clearly be distinguished from those produced by a dissociative NMDA receptor antagonist ((*S*)-ketamine) and a mood activating entactogen (MDMA). These results suggest that the new subscales may be useful to identify more specific experiential features of ASCs and their respective neural correlates.

Specific aspects of ASCs can also be qualified using other psychometric scales. For example, Griffiths and co-workers have shown that psilocybin-induced mystical effects can be assessed with the Mystical Experience Questionnaire (MEQ) (Griffiths et al. 2008). The MEQ is a non-validated self-report measure (Pahnke 1963) covering 7 of the 9 core characteristics of mystical experiences defined by Stace (1961): feelings of unity, transcendence of time and space, noetic

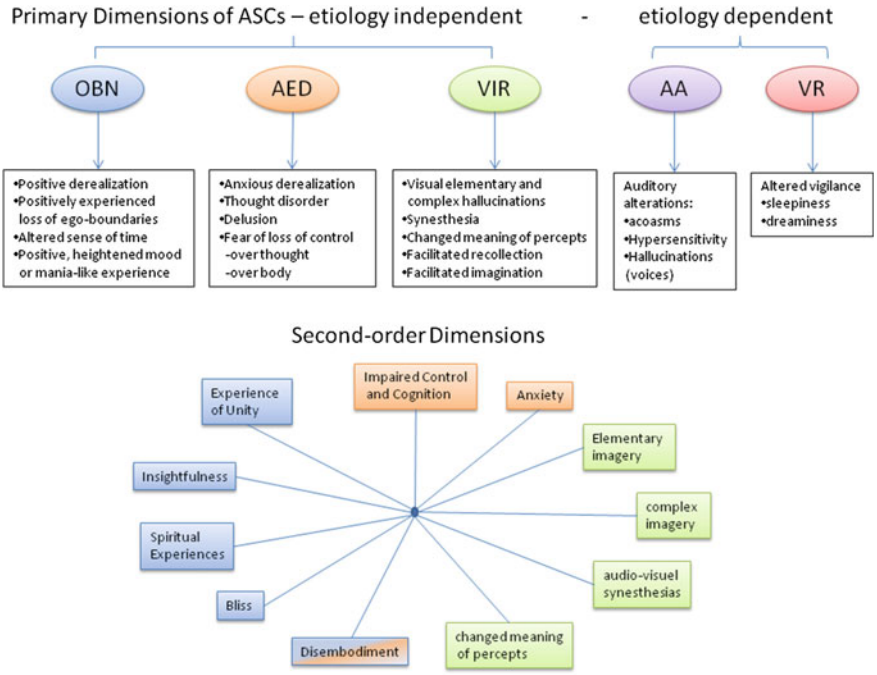

Fig. 1 Structure of altered states of consciousness (ASCs) comprises three primary etiology-independent dimensions/factors: oceanic boundlessness (*OBN*), anxious ego-dissolution (*AED*), and visionary restructuralization (*VIR*), and two etiology-dependent dimensions/factors: acoustic alterations (*AA*) and vigilance reduction (*VR*). The content of these 5 primary dimensions of ASCs can be described by their respective item clusters. According to Studerus et al. (2011), the structure of ASCs can also be described by 11 homogenous lower-order factors

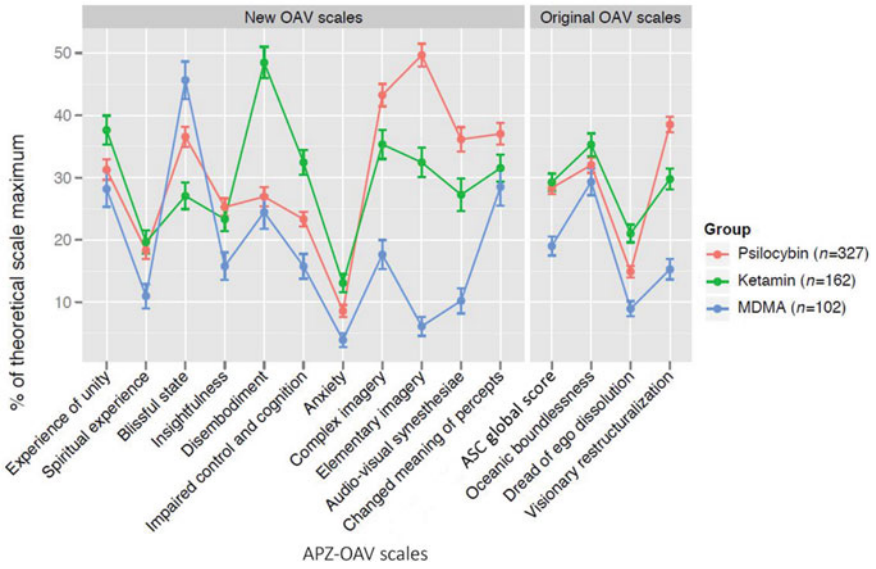

Fig. 2 Known-group validities of the 11 new lower-order and the original APZ-OAV scales (*ASC global score*), oceanic boundlessness (*OBN*), anxious ego-dissolution (*AED*), and visionary restructuralization (*VIR*). *Error bars* represent standard errors (from Studerus et al. 2010)

quality, sacredness, positive mood, ineffability, and paradoxicality. A recent exploratory factor analysis of MEQ data revealed that these characteristic features of mystical states can be reduced to 4 factors covering the MEQ dimensions: F1: unity, noetic quality, and sacredness; F2: positive mood; F3: transcendence of time/space; and F4: ineffability (MacLean et al. 2012). These results indicate that the content of the MEQ dimensions markedly overlaps with the content of OBN dimension and therefore is likely indicative of a specific facet of ASCs.

3 Ego-Dissolution as a Dynamic Process

Several authors have emphasized that the psychedelic experience is not a firmly defined state but rather a dynamic process (Leuner 1962; Masters and Houston 2000). In fact, many of the subjects under the influence of a psychedelic drug appear to progress through different stages over time and levels of changes along a perception-hallucination continuum of increasing arousal and ego-dissolution. Although the intensity, duration, and depth of the stages depend most critically on the dosage, the specific psychedelic drug, and the route of administration, other factors such as personality structure, the nature and dynamics of unconscious material activated, and the expectancy of the subject are also important. Furthermore, the setting—including the physical, cultural, and social environment

and the investigator's theoretical concept, methods, and instructions used—also appears to influence the outcome of the experience.

The psychedelic experience can be conceptualized as having two interrelated components: the experiential content and the experiential process. At the core of this process is the loosening of self-boundaries and the diminishing of ordinary ego-functions, which unfolds along a perception-hallucination continuum with increasing arousal, culminating in ego-dissolution and a state of oneness with the external world. The phenomenological ego as used here is the internal image of a person-as-a-whole, the "I" or "self" as it appears in conscious experience. According to Metzinger (2009), the ego is the content of a self-model; this conscious self-model constructed by the brain allows us to interact with our internal world as well as with the external environment in a holistic manner. In a broad sense, the self encompasses features such as a first-person perspective, feelings of agency, ownership ("mineness") and immediacy ("nowness"), spatial perspective, autobiographical memory, emotions, perceptions, thoughts and acts of will, as well as the feeling of being embedded in our bodily sensations (Metzinger 2009; Northoff 2011). Another function of the ego serves is to help control and plan our behavior and to understand the behavior of others. By representing the process of representation itself, we can catch ourselves in the act of knowing. Ultimately, the subjective experience of the ego arises from dynamic self-related information processing, which is the result of a self-organizing brain system interacting with its environment, because no such things as selves exist in the world (Metzinger 2009).

According to Masters and Houston (2000), modified after (Austin 1998), the dropout of the phenomenological self/ego and ego-functions arises sequentially and unfolds to various degrees along with alterations at: (1) the perceptual level, (2) the recollective–psychodynamic level, (3) the symbolic existential level, and (4) the deep integral level of self-transcendence (Fig. 3).

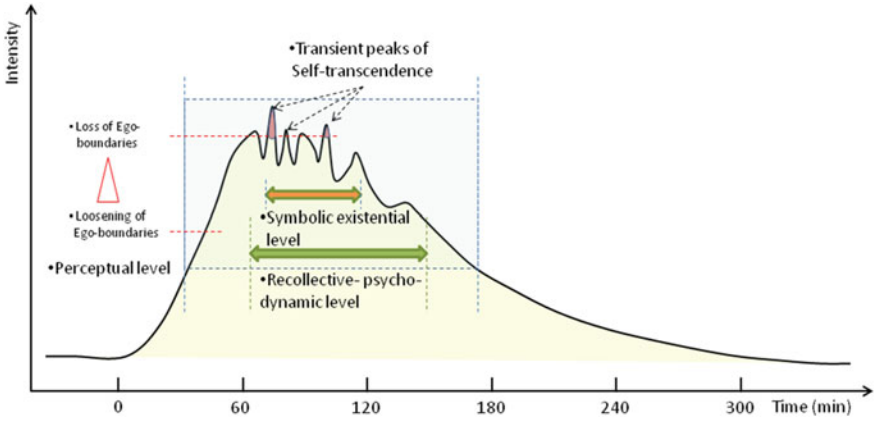

Fig. 3 Temporal dynamics and stages of a psilocybin-induced psychedelic experience. Adapted from Leuner (1962)

Perceptual changes appear with the onset of the reaction to psilocybin or LSD and are the most frequent and robust features of the psychedelic experience. Although perceptual changes can occur in all sensory modalities, the perceptual effects are dominated by visual phenomena, ranging from vividly colored, rapidly moving, and evolving elementary geometric figures to complex images and scenes involving persons, animals, architecture, or landscapes. Neither type has much meaning or function for subjects. In parallel, transformations of the environment and alterations of the body image are frequently reported.

Recollective–psychodynamic level: With increasing arousal toward and during the peak experience, visual images become more personalized, and boundaries between consciousness and unconsciousness dissolve, causing recall and re-enacting of past experiences and memories and releasing emotions into the process. Many of the phenomena and processes occurring at this level can be understood according to concepts of psychoanalytic theory.

Symbolic existential level: In the subsequent level, approaching the peak effects, ideas, eidetic images, or even the entire environment can become symbolized. Subjects become more personally involved and emotionally engaged as a participant in the ongoing psychedelic scenario, also referred to as a symbolic drama. The themes often have mythological and ritualistic overtones, and subjects may identify features of their own existence in legendary historical figures, fairy tales, and archetypal themes or other symbols and play out their personal drama on these allegoric terms. When the subjects encounter and struggle with these dramas, they can achieve a "solution," e.g., by imagination, ideation, sensations, and affective or kinesthetic involvement. This can result in a quiet but powerful emotional response and tension release that appears to be transformative and beneficial to the person. Although ego-boundaries are often transiently markedly reduced or may even disappear for seconds or minutes during these states, subjects are still aware of the situation and its ambiguity.

Deep integral level of self-transcendence: Along with the increasing dissolution of the ego, the psychedelic experience can peak in a state where subjects can become immersed for seconds or minutes in a profound awareness of oneness in which all boundaries disappear and objects are unified into a totality. When subjects have their eyes open, they retrospectively describe this state as an intense emotionally charged new and unfamiliar perspective, almost like a direct encounter with the "ultimate" reality, which can inspire feelings of awe, sacredness, and eternity. This novel experience is also characterized by a pervasive sense of deep insight into the nature and structure of the universe that is far beyond the person's usual mode of thinking. This intuitive awareness of unity appears to resemble the quality of "suchness" as described in states of awakening in advanced Zen mediation (Austin 1998) or as reported in the so-called extrovertive type of mystical states (Stace 1961; Forman 1990). However, when subjects have their eyes closed and turn their attention inward, a state of internal absorption may unfold, with subjects witnessing a vast internal space of objectless infinity that lacks not only the sense of the self, but also all sensory experiences and distracting thoughts. This very rare and transient state of extraordinary absorption is also an essential quality of advanced states

in various forms of concentrative mediation (Austin 1998, 2006) and may reflect what has been termed as the "pure consciousness event" or as the introvertive type of mystical experience in the philosophy of religion (Forman 1990). Such deep integral levels of self-transcendence occur in mature and emotionally stable persons after repeated psychedelic experiences and after subjects have worked through their psychodynamic levels (Grof 1975; Leuner 1962, 1971; Leuner et al. 1994; Masters and Houston 2000).

In general, both the intensity of the psychedelic experience and the loosening of ego-boundaries are dose-dependent, so that ego-dissolution involving disorientation in person, place, and time is rarely induced by medium doses of psilocybin (15–25 mg po) or LSD (100–250 μg po) (Leuner 1962, 1971). However, the same dose may produce more psychotic ego-dissolution, including disorganization, fear, and paranoid ideation, in the same person on different occasions.

According to Leuner (1962, 1981), the type and course of ego-dissolution is driven by four key processes: increasing internal sensory stimulus production, activation of basic emotions and autobiographic memories, regression of ego-functions, and auto-production of symbolic imagery (and meaning). Leuner emphasized that low-to-medium doses of psilocybin or LSD primarily result in a reduction in ego-boundaries and in a "normal and scenic" type of ego-dissolution, which is characterized by vivid imagery and an intensification of affect that is accompanied by intact and adequate emotion processing and by a coherent though expanded "observing" self. In contrast, the "fragmentary or psychotic" type of ego-dissolution that mainly occurs after higher doses (psilocybin >25 mg po; LSD >250 μg po) is dominated by sensory overload including frightening symbolic imagery and excessive affective activation (i.e., "emotional overdrive"); such effects lead, in turn, to disruption of emotional and cognitive integrity, and subsequently to the experience of a fragmented and endangered self, often resulting in feelings of anxiety or panic.

The impact of various psilocybin doses (45–315 mg/kg po) on the two types of ego-dissolution was assessed in healthy volunteers using the "oceanic boundlessness" and "anxious ego-dissolution" 5D-ASC dimensions and is exemplified in Fig. 4.

The neural underpinnings of these two types of ego-dissolution (as indexed by "oceanic boundlessness" and "anxious ego-dissolution") induced by different hallucinogenic drugs have been investigated using PET neuroimaging with the radiotracer ^{18}F-fluorodeoxyglucose (^{18}FDG) (Vollenweider et al. 1997a, b, c). Correlational analysis between normalized metabolic activity and psychological scores on the APZ questionnaire revealed that the magnitude of OBN scores induced by both psilocybin and ketamine correlated positively with regional cerebral metabolic rate of glucose (CMRglu) bilaterally in frontomedial superior, frontolateral, and left inferolateral prefrontal cortex, anterior cingulate, as well as bilaterally in inferior parietal and occipitomedial cortex (Vollenweider and Geyer 2001). There were negative correlations between OBN and CMRglu bilaterally in the hippocampus and caudate nucleus, and left amygdala and ventral striatum. The severity of anxious ego-dissolution was positively correlated with CMRglu in the

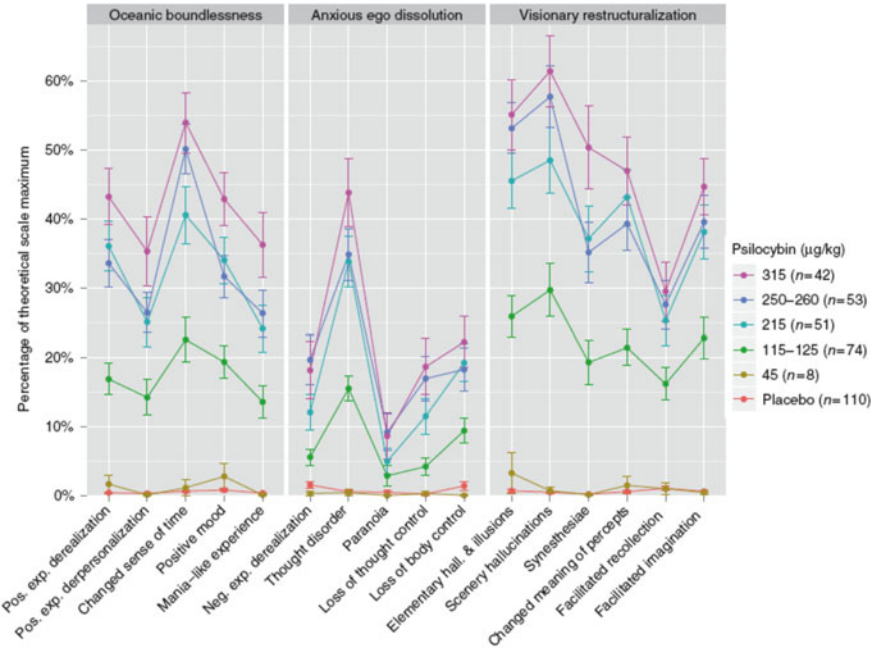

Fig. 4 Dose-dependent percentage scores of item clusters of the 3 etiology-independent primary dimensions: oceanic boundlessness (*OBN*), anxious ego-dissolution (*AED*), and visionary restructuralization (*VIR*) of the 5D-ASC rating scale. Error bars represent standard errors. Ratings were obtained during peak drug effects (60–270 min after drug administration). From Studerus et al. (2011)

thalamus and left temporomedial gyrus and negatively correlated with CMRglu bilaterally in orbitofrontal cortex and adjacent anterior cingulate. Thus, it appears that AED and the associated thought disorder depend mainly on thalamic overactivity and orbitofrontal underactivity. The hyperfrontality finding in ASC was further supported by further brain imaging studies in healthy subjects treated with the classic phenylethylamine hallucinogen mescaline, as well as with psilocybin and DMT (Gouzoulis et al. 1997; Hermle et al. 1993; Riba et al. 2006).

4 Sensory Perception

4.1 Visual Perception

Visual alterations, ranging from illusions to pseudohallucinations, and hallucinations, are a prominent feature of the psilocybin-induced ASC (Studerus et al. 2011; Díaz 2010). However, alterations of visual perception induced by psilocybin rarely represent true hallucinations, since they can usually be distinguished from real

perceptions, at least at moderate doses. Phenomena that are often described include the perception of more intense colors and textures, geometric shapes, rhythmic movements of objects, micropsia and macropsia, after images of objects in movement, and objects, animals, or subjects which are not present (Díaz 2010).

Several experimental studies have described hallucinogen-induced illusions. Siegel and Jarvik (1975) reported that low doses of hallucinogens induced an increase in the subjective brightness of surrounding objects and colors, whereas at medium doses, objects also appeared to drift and pulsate (Fischer and Rockey 1967; Fischer et al. 1969a). Increased brightness in response to visual stimulation after psilocybin intake may be related to an increased P1 amplitude (Kometer et al. 2011).

Increased responsiveness to visual stimuli was related to a reduction in sensory thresholds (Hill et al. 1969; Fischer and Rockey 1967), which might contribute to subjects reporting that everything looks new, fascinating, and more intense (Díaz 2010). However, there are also reports of elevated visual thresholds after LSD (Silverman 1971). These apparent contradictory findings were thought to be due to differences in stimulus intensity: Serotonergic hallucinogens may induce a hypersensitivity to low-to-moderate intensity stimuli, but increased tolerance to high-intensity stimuli (Silverman 1971). However, these assumptions still have to be tested experimentally.

The elementary visual hallucinations induced by serotonergic hallucinogens are often characterized by geometric shapes with rhythmic kaleidoscopic and automatic movement (Díaz 2010). Additionally, the occurrence of simple phosphene-like visualizations such as blobs and light flashes has been described (Shanon 2002; Knoll et al. 1963). Furthermore, a recent study investigating imagination after the intake of moderate doses of LSD found that the vividness/realism of suggested scenarios was significantly higher for the LSD than the placebo condition (Carhart-Harris et al. 2015). These visual alterations were investigated in early work performed by Klüver (1966) and are classified as elementary geometrical patterns known as "form constants" (Siegel and Jarvik 1975; Siegel 1977; see Chapter Kometer and Vollenweider). Furthermore, alterations of motion perception and binocular rivalry are induced by psilocybin (Carter et al. 2005, 2007). Increased completion of partially deleted text as well as reduced object completion of Kanizsa figures was also reported to occur during psilocybin's peak effect (Fischer and Rockey 1967; Kometer et al. 2011). Furthermore, an enlargement of nearby visual space, as inferred from changes of apparent frontal plane (AFP) curve and an enlargement of handwriting area, was measured in psilocybin states (Fischer et al. 1970; Fischer and Mead 1966). This phenomenon was linked to an elevation of the so-called apparent horizon after the intake of LSD (Krus et al. 1963, 1966; Knoll et al. 1963). Under the influence of psilocybin, optical distortions induced by prism spectacles were interpreted as a transformation or unlearning of perceptual constancies that are important for maintaining the stability of the world (Fischer et al. 1970). Fischer et al. (1970) suggested that in psychedelic states the subject's perception is more and more dependent on the projection of central nervous system activity, while outside information is gradually reduced along the

perception-hallucination continuum (Fischer et al. 1970). A similar shift in processing of external versus internal stimuli was suggested by Kometer et al. (2013).

Compared to elementary hallucinations, complex hallucinations are not as frequently reported to be experienced after psilocybin or LSD intake (Kometer et al. 2011; Studerus et al. 2011; Schmid et al. 2015). Complex hallucinations comprise objects, animals, or people and contain more semantic content in comparison with elementary hallucinations (Díaz 2010; Shanon 2002). Additionally, the perception of whole scenes and landscapes has been described (Shanon 2002; Leuner 1962). However, the content varies largely within and between subjects and may even differ between cultures (Díaz 2010). Complex hallucinatory content related to autobiographic memory or personal life situation has also been reported (Dittrich 1998; Studerus et al. 2011). Therefore, visual alterations induced by serotonergic hallucinogens are connected to emotional processing systems and contribute to changes in the meaning of percepts. Hence, they may represent significant experiences for participants. Alterations in the perception of the surroundings associated with feelings of unreality have also been termed "derealization phenomena."

4.2 Auditory Perception

Psilocybin and LSD have been shown to alter auditory perception to a lesser extent than visual perception (Leuner 1962; Studerus et al. 2011; Grof 1975). Studerus et al. (2011) reported that the auditory alterations scale of the 5D-ASC was only moderately affected by psilocybin, since true auditory hallucinations such as hearing voices rarely occurred at the moderate doses tested (Leuner 1962). The auditory alterations mostly comprised intensification of sounds or misperceptions of real auditory stimuli. Fischer et al. (1951) described the occurrence of LSD-induced auditory illusions, such as the perception of rustling noises or perceived alterations of the subject's own voice. Weber (1967) reported that musicians listening to music after ingesting psilocybin described an intensive, exhilarating sound experience. However, the dynamic structure of the music was reported to be difficult to comprehend, which possibly relates to disruptions of time perception (see below). Silverman (1971) measured lower thresholds to auditory stimuli, but also increased tolerance for strong auditory simulation, after the intake of 50 μg LSD. Furthermore, a psilocybin-induced reduction in the N1 sensory ERP in an auditory paradigm was reported, which suggests a reduced processing of the intensity of auditory stimuli (Umbricht et al. 2003). Additionally, psilocybin neither reduced mismatch negativity (MMN) amplitude nor implicit perceptual learning indexed by the frontal memory trace in classical and roving auditory MMN paradigms (Schmidt et al. 2012; Umbricht et al. 2003). These results indicate that psilocybin does not influence auditory processing and sensory learning at moderate doses. However, it is possible that higher doses are necessary to induce alterations in auditory processing. In line with these results, animal studies suggest that disruptive

effects of serotonergic hallucinogens are observed on visual tasks at lower dosages than on auditory tasks (Silverman 1971; Caldwell and Domino 1967). However, a direct comparison in humans is still missing.

4.3 Tactile Perception

Participants reported of tickling sensations in hands and feet and sensations of warmth and cold after LSD intake (Leuner 1962). Furthermore, alterations of body experiences and body scheme, particularly in the perception of extremities, are common (Grof 1975). For example, participants reported muscular tension and feelings of heaviness in the limbs (Hermle et al. 1992). Furthermore, hands and arms were perceived as larger than normal (Leuner 1962; Fischer et al. 1951). Additionally, participants reported feelings of separation from body parts, e.g., the hand was perceived as belonging to someone else (Leuner 1962). Therefore, altered somatic experiences occurring after the intake of serotonergic hallucinogens are closely linked to alterations in self-experience (see above), as well as to detachment from reality and the observed self, which is often summarized under the term "depersonalization phenomena." In experimental studies, tolerance for painful stimulation was found to be elevated after the intake of LSD (Kast and Collins 1964).

4.4 Olfactory and Gustatory Perception

Moderate doses of psilocybin dose-dependently reduced the amount of sodium saccharinate necessary for the detection of taste (Fischer 1967; Fischer and Kaelbling 1966; Fischer et al. 1965a). However, there are also reports of blunted olfactory and gustatory perception after the intake of LSD (Fischer et al. 1951). Olfactory or gustatory hallucinations are more commonly described in terms of synesthesia experiences (see below).

4.5 Synesthesia

Synesthesia experiences are reported to be a common feature of psilocybin- and LSD-induced experiences, occurring even at low doses (Studerus et al. 2011; Schmid et al. 2015). Particularly after ingestion of LSD, audio-visual synesthesias are one of the most prominent experiences (Schmid et al. 2015). After ingestion of LSD, increased visual imagery with eyes closed has been reported to be associated with increased functional connectivity between the visual cortex and the parahippocampus (Kaelen et al. 2016). Music and sounds are most often reported to induce

synesthesia, but tactile, gustatory, olfactory, or emotional stimuli can also induce synesthesia, with the stimuli primarily being translated to the visual domain (Sinke et al. 2012). An experience that is only found in drug-induced synesthesia is the perception of an altered body image (e.g., the body morphs in form and size) in response to visual, acoustical, or tactile stimuli (Sinke et al. 2012). Additionally, synesthesia comprising more than one modality has been described. Leuner (1962) described a visual–tactil–olfactory synesthesia experience: One subject reported that the blue color of a visual stimulus was associated with the perception of an ozone-like smell and the feeling of being electrically shocked. In contrast to acquired and genuine synesthesias, drug-induced synesthesias are highly dynamic and more flexible and show a high inter- and intrapersonal variance (Sinke et al. 2012). This may be one reason why experimental studies investigating drug-induced synesthesias and their underlying neural processes are very rare (Brogaard 2013).

5 Emotion

Serotonergic hallucinogens have been used in psychotherapy since the 1950s to facilitate emotional insight (Sandison and Whitelaw 1957). Various authors (Leuner 1971, 1962; Unger 1963; Johnson et al. 2008; Grof 1975) reported that psilocybin and LSD can intensify all forms of affective responses and may activate vivid memory traces with pronounced emotional undertones. In line with those findings, depressive patients made more personal statements when treated with low doses of LSD (Dahlberg and Jaffe 1979). Descriptions of LSD-induced experiences emphasized a state of euphoria that can take different forms, such as exhilarated elation with unmotivated laughter, deep feelings of peace, exuberant joy, and hedonistic pleasure (Grof 1975; Leuner 1962). Studerus et al. (2011) showed that psilocybin significantly increased heightened mood, emotional excitation, and sensitivity during the peak of the drug effect (60–95 min after administration) on the EWL affective mood rating scale in a large sample of 110 healthy subjects. Recently, Schmid et al. (2015) reported that LSD similarly increased emotional excitation and well-being in 16 healthy volunteers. Recent studies indicate that psilocybin selectively attenuates the encoding and processing of negative stimuli such as negative facial expressions and increases goal-directed behavior toward positive compared with negative cues (Kometer et al. 2012; Schmidt et al. 2013). Using EEG, it was shown that psilocybin valence-dependently decreases the P300 component (Kometer et al. 2012) and the N170 component of the ERP in response to fearful faces (Schmidt et al. 2013). These studies suggest that 5-HT2A receptor stimulation by psilocybin may exhibit antidepressive properties and may have the potential to normalize dysfunctional negative emotional biases (Vollenweider and Kometer 2010). A recent fMRI study corroborates this view by showing that psilocybin reduces amygdala reactivity to negative stimuli and that this attenuation is related to an increase of positive mood in healthy participants (Kraehenmann

et al. 2014). Furthermore, it has been shown that psilocybin augments subjective and neural responses to positive autobiographical memory cues (Carhart-Harris et al. 2012b). Recently, the lasting antidepressive and anxiolytic potential of LSD and psilocybin has received support through the use of psychedelics as adjuncts in the psychotherapeutic treatment of depression and anxiety in patients with life-threatening diseases (Grob et al. 2011; Gasser et al. 2014, 2015).

Although psilocybin can induce very positive and sometimes even mystical-type experiences in healthy volunteers over a large dose range (0.115–0.315 mg/kg), it can also occasionally evoke frightening and unpleasant thoughts, memories, and emotions (Studerus et al. 2011). Within that dose range, unpleasant emotional responses were mostly transient and related to the fear of losing control; such effects can be attenuated by personal support (Johnson et al. 2008; Studerus et al. 2011; Kometer et al. 2012). However, the incidence for anxiety and panic increases with higher doses of psilocybin (Griffiths et al. 2006; Leuner 1971).

6 Cognition

There are numerous anecdotal reports of impaired attention and disturbed cognitive functioning after use of serotonergic hallucinogens (Leuner 1962, 1971). Leuner (1962) found that thinking was experienced as less target-orientated and the integration and linking of thoughts was reported to be difficult after ingestion of LSD. Self-ratings on the 5D-ASC questionnaire confirm that psilocybin can induce a subjective reduction in cognitive functioning (Studerus et al. 2011; Vollenweider et al. 2007; Hasler et al. 2004). Studies testing cognitive functions objectively revealed that psilocybin produces impairments of attention, working memory, and associative learning, while executive functions remain mostly unaffected (Carter et al. 2005; Quednow et al. 2012; Vollenweider et al. 2007; Geyer and Vollenweider 2008; Vollenweider et al. 1998). Therefore, psilocybin induces behavioral impairments in healthy subjects that mimic those seen in the earliest phases of schizophrenia, supporting the idea that serotonergic hallucinogens provide a model psychosis (Geyer and Vollenweider 2008). Several early studies showed that LSD prolonged the time participants required to solve arithmetic problems and impaired performance on the Raven Progressive Matrices Test and inhibitory performance on the Stroop Test (Krus et al. 1963; Wapner and Krus 1960). The later finding was replicated using psilocybin (Quednow et al. 2012). In addition to consistently slowing reaction times (Gouzoulis-Mayfrank et al. 2002; Gouzoulis-Mayfrank et al. 1998b; Quednow et al. 2012; Spitzer et al. 1996), psilocybin impairs sustained attentional performance on the Frankfurter Attention Inventory in a dose-dependent manner (Vollenweider et al. 2007). Psilocybin also impairs attentional tracking ability on a multiple object tracking tasks, an effect that may reflect a reduction in the ability to suppress or ignore distracting stimuli (Carter et al. 2005). Furthermore, psilocybin reduces binocular rivalry switch rate, which seems to be linked to reductions in arousal and attentional functions

(Carter et al. 2007). In line with those results, Gouzoulis-Mayfrank et al. (2002) also reported a psilocybin-induced deficit of response inhibition and difficulties in disengaging attention from previously attended locations. Furthermore, psilocybin triggered deficits in the AX-Continuous Performance Task that were characterized by a failure to use contextual information (Umbricht et al. 2003). Spatial working memory is reportedly impaired after high doses of psilocybin (250 μg/kg) (Wittmann et al. 2007; Vollenweider et al. 1998), but not after administration of lower doses (215 μg/kg) (Carter et al. 2005). Moreover, psilocybin has been shown to induce an increased indirect semantic priming effect, which may be due to a decreased capacity to use contextual information to focus semantic processing (Spitzer et al. 1996). Increased indirect semantic priming has also been observed in schizophrenia patients and has been linked with formal thought disorder (Spitzer et al. 1993). Vollenweider et al. (1998) showed that psilocybin-induced working memory deficits, but not attentional deficits (Carter et al. 2005, 2007), are due to excessive 5-HT2A receptor stimulation. Further studies also revealed that the ability of psilocybin to disrupt inhibition and attentional control measured with the Color Word Stroop Interference Test are attenuated by pretreatment with ketanserin or lamotrigine, indicating that those effects are attributable to 5-HT2A receptor stimulation and suggesting downstream effects on the glutamate system (Quednow et al. 2012; Vollenweider 2008).

A further aspect of cognition is creativity. Since the 1960s, there have been various reports of artists and musicians, as well as scientists and entrepreneurs, who either openly proclaim themselves to be "psychedelic artists," or acknowledge the influence of psychedelic drug-enhanced creativity on their work (Sessa 2008). However, if and how creativity is enhanced by the use of psychedelic drugs is still poorly understood (Sessa 2008). The lack of understanding may be caused by various factors; for example, it is not always possible to devise objective criteria that can be used to measure creativity, and therefore, subjective assessments are often made (Amabile 1982). Furthermore, criteria for determining whether something is viewed as being creative may vary over time and the ability of a drug to enhance creativity may not apply to every individual (Fischer and Scheib 1971; Krippner 1977). The interpretation of scientific data is further complicated since by contemporary standards many early studies had methodological flaws, for example, the omission of placebo controls (Berlin et al. 1955). Fischer et al. (Fischer and Rockey 1967; Fischer and Landon 1972) describe the creative state as an excited state that falls within the continuum of arousal ranging from normal waking consciousness to psychotic and ecstatic states. Those authors reported that elevated closure-making, i.e., an accelerated and enhanced transformation of information to meaning, under excitation induced by psilocybin may underlie the creative state. Sessa (2008) also identifies possible creativity-enhancing features of the hallucinogen-induced experience: (1) increase in complexity and openness, challenging the usual ego-bound restraints, and (2) in line with Fischer et al. (Fischer and Scheib 1971), the tendency to assign unique and novel meanings to the experience, together with the feeling of "oneness" with the world.

Fischer and Scheib (1971) tested these assumptions in a study by measuring creativity prior to, at the peak of, and also at the termination of a psilocybin-induced experience. The authors reported that an individual's ability to float in a dreamy state free of anxiety and to find symbolic meaning in a changing environment may be a prerequisite for psilocybin-induced creative experiences. More specifically, they proposed that sensitive and intuitive people with a field-independent cognition style are more likely to have creative experiences during hallucinogenic drug-induced states. Furthermore, the authors categorized subjects as being either creative performers or creative experiencers (creative performances can be recorded and evaluated, whereas creative experiences produce no record due to the fleeting nature of subjective experience). They further distinguished three types of creative experiencers and performers:

1. uncreative individuals.
2. sensitive, creative experiencers who:
   (a) are creative performers without drugs, but are unable to produce aesthetically pleasing art in drug-induced states or
   (b) score low on creativity without drugs but are creative performer in a drug-induced state
3. a minority who have creative hallucinatory experiences and are creative performers (Fischer and Scheib 1971).

Further studies explored the effect of LSD upon the work of graphic artists and found that art critics judged the LSD-influenced paintings as having "greater aesthetic value" than the artists' usual work (Berlin et al. 1955). In a placebo-controlled study, Zegans et al. (1967) investigated the effect of LSD upon creativity in graduate students using several different tests (the Mednick Association Test, the Modified Word Association Test, the Mosaic Design Test, and the Free Association Test). Although the LSD group performed significantly better than the control group on the test assessing the originality of word associations, no other results were statistically significant. The authors concluded that although administration of LSD cannot enhance creativity in a random group of people, it may increase the accessibility of remote ideas and associations (Zegans et al. 1967). These conclusions were later corroborated by a double-blind and placebo-controlled study where psilocybin was administered to healthy volunteers: Psilocybin induced a larger semantic and indirect semantic priming effect than placebo, suggesting an increased availability of remote associations under the influence of psilocybin (Spitzer et al. 1996). Reportedly, this effect is specific for hallucinogenic drugs (Gouzoulis-Mayfrank et al. 1998b). Additionally, an increase in novel, figurative language was reported in patients under the influence of LSD during psychoanalysis (Natale et al. 1978).

In summary, serotonergic hallucinogens can induce creativity-enhancing experiences related to reduced inhibition, increased fluency and flexibility of ideas, and increased visual imagery, empathy, and capacity to restructure problems

(Sessa 2008). Creative individuals may sometimes be able to transform these experiences into a creative work, but it is unlikely that creativity is enhanced by serotonergic hallucinogens in individuals who do not ordinarily show creative behavior (Krippner 1977; Zegans et al. 1967).

7 Time Perception

Even early phenomenological and psychological studies reported that serotonergic hallucinogens produce a strongly altered experience of time and caused misjudgments of elapsed time intervals (Leuner 1962; Heimann 1963; Grof 1975). Participants reported a feeling that the passage of time was speeding up or slowing down, or experienced feelings of timelessness, effects that were often associated with visual perceptual changes and alterations in self-experience (Kenna and Sedman 1964; Heimann 1963; Grof 1975). Heimann believed the psilocybin-induced feeling of time stopping was linked to an inner psychic state involving the loss of serial temporal order and an impairment of the ability to determine causal relationships and serial integration. Additionally, Heimann associated disturbances in time perception with impairments of the coordination and perception of movement (the motion of moving objects was not perceived as being continuous, but rather appeared as a series of discontinuous static images) (Heimann 1994). A reduction in temporal motion integration has also been described in a later placebo-controlled study with psilocybin (Carter et al. 2004). The fact that hallucinogens cause some musicians to feel that they have lost their musical talent may also be a consequence of altered temporal perception. While listening to music or playing music after ingesting psilocybin, musicians reported that sounds were experienced as stretched and that "music was standing still." Furthermore, psilocybin made it difficult for the musicians to distinguish rhythms; the dynamic structure of music was often disturbed, with songs experienced as an unrelated sequence of parallel tones, and temporal coherency was lost (Weber 1967). Using items in the 5D-ASC rating scale related to temporal perception, Studerus (Studerus et al. 2011) confirmed that psilocybin produced a dose-dependent alteration of the sense of time in a large sample of participants (n = 110). Recent studies using standardized measures of temporal processing were able to confirm that psilocybin dose-dependently alters time perception and temporal control of behavior (Wackermann et al. 2008; Wittmann et al. 2007). Wackermann et al. (2008) reported an increase in the loss rate of internal time representation even under a very low dose of psilocybin (12 μg/kg body weight). This study suggests that psilocybin might cause a fusion of the "inner" and "outer" horizons of temporal experience resulting in an impairment of cognitive processing based on temporal order. Recently, a link between the loss rate of duration representations and certain serotonin system genotypes was detected: A higher loss rate was found for the carriers of genotypes known to augment serotoninergic transmission (Sysoeva et al. 2010). In line with an earlier study conducted with LSD

(Aronson et al. 1959), Wittmann et al. (2007) reported that participants underestimated intervals longer than 2.5 s in an interval reproduction task and had an impaired ability to synchronize tapping when inter-beat intervals were longer than 2 s. No impairments were found for shorter time intervals, indicating a potential interaction with cognitive processes such as working memory. Furthermore, individual tapping tempos were slowed down.

8 Non-pharmacological Predictors

Individual reactions to serotonergic hallucinogens vary widely, even when the experimental conditions are maintained constant (Dittrich 1994; Nichols and Chemel 2006). Out of 24 variables analyzed by Studerus et al. (2012), dose was found to be the most important factor predicting the acute response to psilocybin in a large sample of participants (n = 409 trials); however, a large proportion of inter- and intraindividual differences in reactions were also influenced by non-pharmacological variables (Studerus et al. 2012; Grof 1975). Within these factors, an important distinction has been made between "set" and "setting" (Grof 1975; Leary et al. 1963). Set refers to expectations of the subject, their personality structure, and current mood state, whereas setting comprises the specific circumstances in which the drug is administered, e.g., the physical, social, and cultural environment (Leary et al. 1963; Grof 1975). While the earliest academic research on serotonergic hallucinogens was conducted without considering the influence of set and setting, later research included more preparation and interpersonal support and consequently reported fewer adverse psychological reactions (Johnson et al. 2008). The specific effects of set and setting variables are discussed below.

8.1 Demographic Variables

In line with early studies investigating the effects of LSD (Hyde 1960), Studerus et al. (2012) showed that the effects of psilocybin were not moderated by gender. Additionally, neither body mass index nor years of education predicted the psilocybin reaction in the study (Studerus et al. 2011). However, this and previous studies found that older subjects reported less impairment of control and cognition and tended to experience a more blissful state compared with younger subjects, and there was an inverse relationship between age and the likelihood of having an unpleasant and/or anxious reaction to psilocybin or LSD (Hyde 1960; Studerus et al. 2012).

8.2 Personality

Many studies suggest that responses to serotonergic hallucinogens are dependent—at least to some degree—on personality structure (e.g., Fischer et al. 1968; Hemsley and Ward 1985; Dittrich 1994; Lienert and Netter 1996; Thatcher et al. 1971; Silverman 1971). Fischer et al. (1965a, b, 1968; Fischer 1971) reported that taste-sensitive subjects who also tended to be intuitive and introversive were more sensitive to the effects of psilocybin, whereas taste-insensitive, taste-extroversive subjects require larger doses to elicit comparable effects. The authors described the psilocybin-sensitive subjects as being "variable subjects" or "minimizers" with high creativity scores, large handwriting area, large standard deviation on the handwriting area, large retest variance on perceptual tasks, and fast reaction time. In contrast, insensitive subjects were reported to be "stable subjects" or "maximizers" with a small standard deviation and handwriting area, small retest variability, and low creativity scores (Thatcher et al. 1971; Gwynne et al. 1969; Fischer et al. 1969b). Such findings are in line with observations by Leuner (1962) who reported that rational, down to earth, intellectual predispositioned individuals tended to be resistant to hallucinogen-induced intoxication. Leuner concluded that scholarly individuals in particular required higher doses, whereas individuals who were more emotionally guided (e.g., artists or musicians) required lower doses of LSD to produce an experience of the same intensity (Leuner 1962). Additionally, studies conducted using LSD also found that more intense reactions occurred in individuals with introversive or histrionically structured personalities compared with those having extroversive or compulsively structured personalities (Hyde 1960; Buckman 1967; Grof 1975). However, Dittrich (1994) reported that an optimistic, extroversive attitude toward life predicted scores in the oceanic boundlessness (OBN) and visual alteration (VIR) dimensions and the overall intensity of the altered state of consciousness (ASC). This finding is in line with a pilot study conducted by Thatcher et al. (1971), who found that certain extroversive subjects were more strongly affected by psilocybin. A recent study added to these data by showing that subjects who were more sociable (i.e., outgoing and extroverted) reported lower scores on items assessing spiritual experience and higher scores on items assessing audio-visual Synesthesia (Studerus et al. 2012). Furthermore, in the study by Dittrich (1994), a high esthetic sensibility and a non-dogmatic religiosity also predicted the experience of oceanic boundlessness (OBN) and the overall ASC intensity. A high esthetic sensibility was also associated with the occurrence of visual alterations. Furthermore, rigid and emotional unstable subjects were reported to be more at risk for anxious reactions to serotonergic hallucinogens (Lamparter and Dittrich 1994; Dittrich 1994). Several studies found moderate-to-strong correlations between measures of neuroticism and the occurrence of anxious reactions to serotonergic hallucinogens (Dittrich 1994; Hemsley and Ward 1985; Lienert and Netter 1996). Nonetheless, a recent study conducted with a large sample did not detect any statistically significant relationship between Neuroticism–Anxiety scores and negative reactions to psilocybin (Studerus et al. 2012). However, subjects with

very high Neuroticism scores (i.e., scores that were more than two standard deviations above the mean) were excluded from the latter study during the initial screening. Furthermore, the personality trait Absorption (i.e., an individual's openness to a variety of cognitive, perceptual, and imaginary experiences, as well as vivid imagery, synesthesia, and intense involvement in aesthetics and nature) was found to be the second most important predictor after dosing of psilocybin response. The Absorption trait was highly positively correlated with the overall level of consciousness alteration and strongly predicted the occurrence of mystical-type experiences and the intensity of visual effects induced by psilocybin (Studerus et al. 2012). In contrast to previous studies (e.g., Buckman 1967; Dittrich 1994; Fischer et al. 1968), other than absorption, the only personality trait that accurately predicted psilocybin responses was the factor Sociability (i.e., being outgoing and extroverted). Other personality traits made only marginal contributions to the prediction of psilocybin responses (Studerus et al. 2012).

8.3 Mood

Early studies identified mood as an important predictor of the experience induced by hallucinogens (Johnson et al. 2008). For example, Metzner et al. (1965) reported that the best predictor for mood during a psilocybin session was mood prior to the session, e.g., a presession negative mood often resulted in anxious or negative experiences during the session. Dittrich (1994) found that emotional lability, measured as a state variable, predicted higher values on the APZ anxious ego-dissolution (AED) dimension after administration of DMT. Furthermore, Dittrich found that the presence of feelings of calmness in subjects prior to administration of hallucinogens correlated positively with their experience of oceanic boundlessness and visual alterations, as well as with the overall intensity of the ASC (Dittrich 1994). These findings are in line with those of a study recently conducted by Studerus et al. (2012), which found that current mood state and the presence of psychological distress during the past four weeks preceding drug intake were more important for predicting psilocybin responses compared with personality factors. In particular, this study found that emotional excitability shortly before drug intake predicted the occurrence of anxious reactions to psilocybin better than the trait anxiety–depressiveness. Furthermore, measures of performance-related activity (i.e., go-getting, avid, active, and energetic items on the EWL affective mood rating scale) were among the most important predictors of the overall level of consciousness alteration, as well as experiences of oceanic boundlessness (OBN) and visual reconstructualization (VIR) (Studerus et al. 2012). The authors suggested that the items assessing performance-related activity were strongly associated with positive mood and general optimism. Therefore, the authors concluded that being in an emotionally excitable and active state prior to drug intake and having experienced few psychological problems for several preceding weeks increased the intensity of pleasurable and visual experiences (Studerus et al. 2012). Other factors

closely related to mood are peer support and the attitude toward the experiment and the investigator (Johnson et al. 2008). Leuner (1962) reported that the intensity of the response to LSD was influenced by how participants felt regarding the study and the study personnel. Furthermore, peer support and concomitant emotional support provide a benign interpretive context for the hallucinogen experience and therefore can reduce adverse psychological effects (Dunsmore and Kaplan 1997; Leary et al. 1963; Johnson et al. 2008).

8.4 Expectations

The expectations of subjects regarding the effects of hallucinogens can reportedly influence the nature of experience (Dittrich 1994; Leary et al. 1963; Metzner et al. 1965; ten Berge 2002; Unger 1963; Savage et al. 1966) and are probably closely linked to mood preceding the session. For example, although most studies investigating the potential for psychedelic drugs to enhance creativity showed mixed results (see above), Harman et al. (1966) showed that LSD and mescaline enhanced performance in creativity tests that were made in a setting where the expectation that the drug would enhance creativity was reinforced. Additionally, the expectation and attitude of the experimenter or therapist can reportedly influence the hallucinogen-induced experience, probably by inducing similar expectations in the subjects (Savage et al. 1966; Unger 1963). In particular, anxiety in the experimental staff may lead to anxiety-ridden experiences for subjects, whereas calm experimenters may reduce anxiety in participants and patients (Unger 1963). Johnson et al. (2008) recommend careful preparation of participants, which also involves the discussion of expectations—including those that are potentially unrealistic—as well as the study procedures and timing in order to avoid surprises during the session.

8.5 Genetic Factors

Although to date no investigations have directly assessed the influence of genetics on the reaction to psilocybin, several studies suggest that the hallucinogen-induced experience might, at least to some extent, be influenced by genetic factors. It is well established that many effects of serotonergic hallucinogens are attributable to excessive 5-HT2A receptor activation (Quednow et al. 2012; Kometer et al. 2012; 2013; Passie et al. 2002; Vollenweider et al. 1998). The 5-HT2A receptor gene resides on chromosome 13q14–q21; several different gene variants that are associated with functional and clinically relevant effects have been identified (Benedetti et al. 2008; Serretti et al. 2007). These 5-HT2A polymorphisms may contribute to inter-individual differences in response to serotonergic hallucinogens. In particular, Ott et al. (2005) demonstrated that a significant association exists between a T102C polymorphism of the 5-HT2A receptor and the personality trait of Absorption.

Participants with the T/T genotype of the T102C 5-HT2A polymorphism, implying a stronger binding potential of the 5-HT2A receptor, had higher absorption scores. As discussed above, the personality trait of Absorption was found to be an important predictor of psilocybin response (Studerus et al. 2012). Therefore, polymorphisms related to differences in the binding potential of the 5-HT2A receptor, such as the T102C polymorphism, may also contribute to variations in the responsiveness of subjects to hallucinogenic drugs. Furthermore, Sysoeva et al. (2010) reported that the loss rate of duration representation, which has been shown to be altered after administration of psilocybin, is higher for carriers of genotypes that are characterized by enhanced serotonin transmission (e.g., the 5HTLPR SS polymorphism compared to the LL genotype, the "low expression" variant of the MAOA VNTR gene compared to the "high-expression" variant, and the T/T genotype of the T102C polymorphism compared to the C/C genotype). Additionally, further investigations showed an association between T102C polymorphisms and sensorimotor gating (Quednow et al. 2008, 2009), thereby providing a possible link between genetic differences and hallucinogen-induced deficits in prepulse inhibition and cognition. In sum, there is evidence that a common genetic basis may exist for inter-individual differences in serotonergic neurotransmission and for differences in response to hallucinogens. However, the association between these polymorphisms and the phenomenology of hallucinogen-induced experiences has not yet been tested directly and will likely be the subject of further studies.

8.6 Physical Environment

The physical environment in which hallucinogens are administered has been reported to greatly influence the experience and probably has effects on expectations and mood before drug administration (Johnson et al. 2008; Strassman 2001; ten Berge 2002; Grof 1975). Johnson et al. (2008) recommend an aesthetically pleasing and comfortable environment and suggested that "cold" and overly clinical surroundings should be avoided in hallucinogen research in order to reduce the risk of anxious reactions. The environment can directly influence perceptual changes and the possibility of disorientation occurring under the influence of hallucinogens (Johnson et al. 2008; Strassman 2001). Relevant features of the environment include, for example, the furniture of the experimental room and its temperature, odors and fragrances, as well as acoustic stimuli such as music or the ringing of a telephone, which can trigger markedly different experiences (Grof 1975). Therefore, using a safe, familiar environment that minimizes the risk of surprises (e.g., meeting new people, receiving unexpected phone calls) is encouraged (Johnson et al. 2008). These reports are corroborated by Studerus et al. (2011) who investigated the effects of psilocybin administration in a rather technical PET environment versus laboratory rooms furnished in a comfortable, aesthetically pleasing manner. The latter study reported that the PET environment was associated with more anxious reactions; the

absence of distractions in the scanner environment—subjects did not have to interact with peers or complete tasks, for example—may have allowed participants to concentrate on the experience, potentially causing increased confrontation with their inner fears (Studerus et al. 2011). However, even in the PET environment, the percentage of subjects experiencing a strong anxious reaction was still very low. Another factor that helped to create a positive environment was the presence and support of other people (Dunsmore and Kaplan 1997; Johnson et al. 2008; Grof 1975). The inclusion of people from both genders in the monitoring team is recommended to foster feelings of security in the research environment (Johnson et al. 2008; Grof 1975). As mentioned above, the attitude of the experimenter can strongly influence the participant's experience (Unger 1963; Savage et al. 1966). Hyde reported that impersonal, investigative, or hostile attitudes can arouse hostile paranoid responses (Hyde 1960). Alternatively, when the experimenter has the specific intent of making the experience positive, the majority of participants report a positive experience (Metzner et al. 1965; Unger 1963). Therefore, Johnson et al. (2008) emphasized the importance of having a friendly, welcoming, compassionate, and respectful atmosphere supported by all research staff members, as well as a trusting relationship between participant and monitors. Personal support has furthermore been reported to be very effective in reducing anxiety or fear during the course of action of hallucinogens (Johnson et al. 2008; Studerus et al. 2011).

8.7 Previous Experience

It has been reported that prior experience with substances inducing ASCs influences subsequent experiences and probably affects the mood and expectations preceding drug administration (Leuner 1962; Metzner et al. 1965). Various studies report that previous experience with classical hallucinogens is negatively associated with the occurrence of somatic symptoms (Leuner 1962; Studerus et al. 2012). While these symptoms may initially be perceived as disturbing, they recede into the background with more experience (Leuner 1962). Furthermore, Leuner (1962) noted that after several hallucinogen-induced experiences, participants would sometimes require only low doses to elicit experiences of the same intensity. Leuner (1962) named this phenomenon "paradoxical habituation." In line with previous studies (Leuner 1962; Metzner et al. 1965), Studerus et al. (2012) reported that hallucinogen-naïve subjects experienced slightly more visual alterations, disembodiment, and changed meaning of percepts. Furthermore, the intensity of concentration deficits was reported to diminish when subjects had previous experience with hallucinogens (Leuner 1962). However, complex, scenic hallucinations were found to be more likely to occur after repeated hallucinogen administration (Leuner 1962). Furthermore, Dittrich (1994) reported that familiarity with drug-induced ASCs correlated negatively with DMT-induced anxiety and general familiarity with ASCs predicted a higher score on the 5D-ADC oceanic boundlessness scale.

9 Long-Term Effects

Studerus et al. (2011) analyzed long-term follow-up data from 90 subjects that were collected 8–16 months after experimental sessions with psilocybin. The authors reported that the majority of subjects rated the psilocybin experience as enriching or very enriching (92%). In another follow-up study conducted 14 months after administration of a high dose of psilocybin, more than half of the participants even rated the psilocybin-induced experience as being among the five most personally meaningful experiences of their lives (Griffiths et al. 2008).

Studerus et al. (2011) reported that the subjective changes in attitude and personality included positive changes in items measuring the attitude toward ASCs (56% of subjects), relationship to nature (38%), and aesthetic experiences (37%). Enhanced appreciation of art and music was also reported by McGlothlin et al. (1967) in a follow-up assessment conducted six months after an LSD experience. Furthermore, participants engaged in more creative activities such as attending musical events, visiting museums, and buying records. However, no actual increase in creative ability was measured. This finding is in line with results obtained by Dobkin De Rios and Janiger (2003) who found that there was no overall increase in creativity but that certain aspects of artists' work were enhanced after an LSD experience—for example, there may be a tendency toward more expressionistic work, a sharpening of color, or a greater freedom from prescribed mental sets. Additionally, MacLean et al. (2010) reported that the personality trait openness of the NEO Personality Inventory remained significantly elevated one year after the session in participants who had a mystical experience after a high dose of psilocybin. Studerus et al. (2011) reported that a single dose of psilocybin in a non-therapeutic research setting did not significantly affect subsequent drug use patterns. Furthermore, detailed questions about possible flashback phenomena and spontaneous alterations of consciousness revealed that none of the subjects fulfilled the diagnostic criteria for hallucinogen persisting perception disorder (HPPD) in DSM-IV or flashbacks in ICD-10, and the subjects did not report experiencing visual phenomena reminiscent of the typical symptoms of HPPD (Studerus et al. 2011). This is in line with the findings of Johnson et al. (2008) who reported that the incidence of lasting perceptual abnormalities is much lower in research contexts compared to illicit recreational use due to careful screening and preparation of subjects.

10 Biological Models of ASCs

Numerous authors have proposed models to explain the biological underpinnings of ASCs in order to account for the symptoms experienced after administration of hallucinogens as well as the nature of human consciousness (Fischer 1971; Geyer and Vollenweider 2008; Tononi 2004; Vollenweider and Geyer 2001).

Early studies conducted by Fischer and colleagues led them to propose a psychophysiological model of ecstatic and meditative states that also addressed psychedelic experiences (Fischer 1971). According to their model, ecstatic states can be mapped on a continuum of increasing arousal ranging from normal perception to hallucinations. Hallucinogen-induced states are characterized by an increase in the amount of sensory information that is not offset by a corresponding increase in the rate of information processing. Consequently, as the amount of externally and internally generated stimuli increases, exteroception gradually shifts to interoception. Fischer supported his model by demonstrating elevated ratios of sensory-to-motor activity using various psychophysiological measurements (e.g., Fischer et al. 1965a, 1969a, 1970; Fischer and Kaelbling 1966; Fischer and Mead 1966). Furthermore, Fischer (1971) described the experience of subjective reality as an interpretation of CNS activity within a structure of learned constancies, i.e., a learned model of a world ordered and stabilized by self-programmed rules. Moving along the continuum causes an "unlearning" of constancies due to an arousal-induced transformation, which gives rise to the effects seen in the hallucinogen intoxication. With increasing levels of arousal, the "I" of the physical world gives way to the "Self" of the mental dimension and the level of external sensory information reaching the brain is gradually reduced.

More recent evidence from animal and human studies suggests that serotonergic hallucinogens disrupt information processing in cortico–striato–thalamocortical (CSTC) feedback loops, which have been implicated in gating the flow of sensory and sensorimotor information to the cortex (Vollenweider and Geyer 2001; Geyer and Vollenweider 2008). The so-called CSTC information processing model proposes that deficits in early information processing may underlie the alterations of perception, cognition, and the sense of self that occur in psychedelic states (Vollenweider and Geyer 2001). According to this model, the inability to filter, inhibit, and gate exteroceptive and interoceptive stimuli may lead to cortical sensory overload and subsequently to a breakdown of cognitive integrity, resulting in hallucinations and alterations of ego-functioning. Deficits in preattentive sensorimotor gating have repeatedly been reported after psilocybin and LSD administration (Quednow et al. 2012; Schmid et al. 2015; Vollenweider et al. 2007) and have been related to alterations in cognitive functioning (Quednow et al. 2012; Vollenweider et al. 2007). The CSTC model proposes that the thalamus plays a key role within the CSTC feedback loops for gating external and internal information to the cortex and, thereby, is crucially involved in the regulation of the level of awareness and attention (Geyer and Vollenweider 2008; Vollenweider et al. 2007). This view is in line with the information integration theory of consciousness (Tononi 2004), which proposed that the thalamus and thalamocortical systems play a key role in integrating information processing and the ensuing consciousness. Serotonergic hallucinogens may alter thalamocortical transmission by stimulation of 5-HT2A receptors located at multiple sites within the CSTC loops (Geyer and Vollenweider 2008; Vollenweider et al. 2007). Indeed, PET and SPECT

neuroimaging studies have shown that oral administration of psilocybin, mescaline, and DMT can alter neuronal activity in frontomedial and frontolateral cortices ("hyperfrontality"), basal ganglia, and thalamus (Vollenweider et al. 1997c; Gouzoulis-Mayfrank et al. 1999; Hermle et al. 1993; Riba et al. 2006), effects that are variously correlated with different dimensions of the psychedelic state (see above). Nevertheless, a recent fMRI study reported a decrease in brain activity in the medial frontal cortex after intravenous administration of psilocybin (Carhart-Harris et al. 2012a). However, numerous factors (differences in the route of administration (i.v. vs. p.o.), the indices used to monitor neuronal activity (metabolic rate of glucose, CBF, BOLD), or the intensity and content of psilocybin-induced symptoms) could account for these apparent discrepancies. Much additional research is needed to gain a better insight in the relationship between subjective experience in psychedelic states and neuronal activity in humans, especially given the complexity and variability of psychedelic experiences.

More recently, an "entropic brain hypothesis" was proposed based on the effects of intravenous administration of psilocybin measured using fMRI and MEG techniques (Tagliazucchi et al. 2014; Carhart-Harris et al. 2012a, 2013, 2014; Muthukumaraswamy et al. 2013). The model proposes that various conscious states are related to entropy measures of brain activity by an inverted-U-shaped function. Whereas sedation and anesthesia reflect rigid, low-entropy states, psychedelic states are characterized by increased flexibility and high entropy, which is associated with more random brain activity and flexible cognition (Carhart-Harris et al. 2014). Those authors corroborated their model with studies showing that psilocybin produces an increase in BOLD signal variance, a greater diversity of connectivity motifs in a hippocampal/ACC network, decreased connectivity within the default mode network (DMN), a reduction in DMN-TPN anticorrelation, and desynchronization of cortical oscillatory rhythms (Carhart-Harris et al. 2012a, 2013; Muthukumaraswamy et al. 2013; Tagliazucchi et al. 2014). The authors concluded that a disorganization of brain activity underlies hallucinogen-induced ASCs (Carhart-Harris et al. 2014).

In summary, numerous models have been proposed emphasizing different aspects and focusing on different neurobiological correlates of ASC. These models are not mutually exclusive, but are probably not able to capture the diverse and dynamic effects induced by hallucinogens when considered separately. More research on all levels of the hallucinogenic action (from receptors over brain networks to psychological effects) is needed to develop a unified and comprehensive biological model of ASC.

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