Serotonergic Hallucinogen-Induced Visual Perceptual Alterations

Michael Kometer and Franz X. Vollenweider

Abstract Serotonergic hallucinogens, such as lysergic acid diethylamide (LSD), psilocybin, and *N*,*N*-dimethyltryptamine (DMT), are famous for their capacity to temporally and profoundly alter an individual's visual experiences. These visual alterations show consistent attributes despite large inter- and intra-individual variances. Many reports document a common perception of colors as more saturated, with increased brightness and contrast in the environment ("Visual Intensifications"). Environmental objects might be altered in size ("Visual illusions") or take on a modified and special meaning for the subject ("Altered self-reference"). Subjects may perceive light flashes or geometrical figures containing recurrent patterns ("Elementary imagery and hallucinations") influenced by auditory stimuli ("Audiovisual synesthesia"), or they may envision images of people, animals, or landscapes ("Complex imagery and hallucinations") without any physical stimuli supporting their percepts. This wide assortment of visual phenomena suggests that one single neuropsychopharmacological mechanism is unlikely to explain such vast phenomenological diversity. Starting with mechanisms that act at the cellular level, the key role of 5-HT2A receptor activation and the subsequent increased cortical excitation will be considered. Next, it will be shown that area specific anatomical and dynamical features link increased excitation to the specific visual contents of hallucinations. The decrease of alpha oscillations by hallucinogens will then be introduced as a systemic mechanism for amplifying internal-driven excitation that overwhelms stimulus-induced excitations. Finally, the hallucinogen-induced parallel decrease of the N170 visual evoked potential and increased medial P1 potential will be discussed as key mechanisms for inducing a dysbalance between global

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integration and early visual gain that may explain several hallucinogen-induced visual experiences, including visual hallucinations, illusions, and intensifications.

Keywords Hallucination · Imagery · Hallucinogen · Psilocybin · LSD · Ayahuasca

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1 Introduction

The dramatic visionary impact of serotonergic hallucinogens has prompted their use across various cultures and throughout time, discerned in rock paintings and symbolic cultural materials dating back thousands of years. Notably, these visual expressions frequently resemble forms that are characteristics of the elementary visual hallucinations seen in drug-induced states (Kroeber 1925; Lewis-Williams et al. 1988; Winkelman 2002). In line with this idea, several visual artists have claimed that serotonergic hallucinogens greatly increased their visual creativity, allowing a connection between the artist and comparatively subconscious, internal aspects of vision (Berlin et al. 1955; Krippner 1985; Janiger and de Rios 1989; Grey and Wilber 2001). The strong link between hallucinogens-induced visual percepts, emotions, and autobiographic memory has further been exploited in psycholytic or psychedelic therapy in western society (Leuner 1967; Grof 1973; Grinspoon and Bakalar 1986; Vollenweider and Kometer 2010; Carhart-Harris et al. 2012). Similarly, shamans have been taken advantages of hallucinogen-induced imagery/hallucinations to influence illness processes since a long time (Achterberg 1987; Mercante 2006; Achterberg 2013). Finally, hallucinogen-induced visual perceptual alterations have been assessed using modern brain imaging techniques to elucidate the neuropsychopharmacological mechanisms of visual perceptual alteration and thereby gain insights into functional properties of the visual

system and the pathophysiology of visual hallucinations (Kometer et al. 2011, 2013).

Given the cross-cultural influence of the visionary properties of serotonergic hallucinogens, Sect. 2 will review the phenomenology and psychology of drug-induced perceptual alterations, as well as their cultural determinants. Next, Sect. 3 will introduce several neural mechanisms that potentially underlie the rich visual phenomenology of serotonergic hallucinogens, ranging from mechanisms with actions at the cellular level to mechanisms with actions at the whole-brain level.

2 Phenomenology and Psychology

2.1 Visual Illusions, Distortions, and Intensifications

Serotonergic hallucinogens induce several visual percepts that are driven by the environment, but are characterized by an increased mismatch to the actual physical constitution of the subject's surroundings. This phenomenon can be appreciated by the altered perception of visual objects as decreased or increased in their perceived versus actual size (Dittrich 1998), or with modified angles (Díaz 2010). Furthermore, objects may rhythmically move or vibrate along their edges (Díaz 2010), which is apparently paralleled by a diminished performance in higher level motion recognition tasks for subjects under the influence of hallucinogens (Carter et al. 2004). Moreover, a subject's discernment of visual space is reportedly transformed after the administration of the serotonergic hallucinogen psilocybin, as evidenced by an augmented misjudgment regarding visual depth and the visual vertical or horizontal in tiled body positions (Hill et al. 1968; Fischer et al. 1970; Hill and Fischer 1973).

In addition to these alterations in complex, integrative visual processes (e.g., object recognition and formation of visual space), the perception of elementary visual features (brightness, color saturation, visual contrast) can be subjectively increased by serotonergic hallucinogens (Klüver 1942; Rümmele and Gnirss 1961; Klüver 1966; Dittrich 1998; Díaz 2010). Together with this subjective increase, a hallucinogen-intoxicated individual will show a preference for dimmer light in the room while experiencing the peak of the drug experience (Fischer et al. 1969). Following the administration of hallucinogens, subjects further reported that they could see more colors than usual due to flickering lights or visualization of after-images (Hartman and Hollister 1963).

On the other hand, the accuracy for detecting low-level features in behavioral tests remains mostly unaltered by serotonergic hallucinogens. For example, the threshold for discriminating near-threshold light stimuli was only slightly increased in early investigations of drug effects (Blough 1957; Carlson 1958), whereas color discrimination accuracy was either unaltered (Edwards and Cohen 1961; Hollister

and Hartman 1962) or slightly decreased (Hartman and Hollister 1963). The contrast sensitivity for drifting gratings also stayed the same (Carter et al. 2004). The only clear exception to this detection pattern was an enhanced discrimination accuracy for flickering lights after administration of low-dose serotonergic hallucinogens (Becker et al. 1967). This exception implies that the formation of visual hallucinations and/or cognitive impairments at higher drug doses can prevent the detection of any increased accuracy in visual low-level behavioral tasks. Nonetheless, the overall picture suggests that increasing doses of serotonergic hallucinogens typically induce an augmented mismatch between subjective visual experiences and visual percept accuracy.

2.2 Imagery and Hallucinations

2.2.1 On the Distinctions Between Imagery and Hallucinations

Serotonergic hallucinogens induce several types of visual experiences ranging from imagery and pseudohallucinations to ideal hallucinations that are commonly defined by the absence of sensory input supporting these percepts. Distinctions between these categories were based on visual attributes such as vividness, intensity, appraisal, emotional reaction, volitional control, and sense of reality (Horowitz 1975), but no agreement emerged and instead a continuity between these categories has been proposed (Seitz and Molholm 1947; Horowitz 1975). Most typically, imagery lacks the vividness and intensity of hallucinations, but is more under the control of the subjects. The vividness of imagery is frequently reported to be increased by serotonergic hallucinogens (Dittrich 1998; Studerus et al. 2010), leading to a stage where the visual effects are better characterized as hallucinations. Pseudohallucinations are thought to be as vivid as ideal hallucinations, but are recognized to be self-produced. Although hallucinogen-induced percepts can usually be recognized as self-produced at moderate doses, this capacity seems to diminish with increasing dose (Shanon 2002; Rolland et al. 2014), leading first to a situation in which more time is required to differentiate between self- and external-induced percepts until finally this distinction is no longer possible (Cott and Rock 2008; Luke 2011). Thus, given the continuity between these categories, they will not be strictly differentiated throughout this Chapter. Instead, it seems more useful to note a progression of these visual experiences toward more vividness, intensity, and sensed reality with increasing doses (Shanon 2002). A clearer distinction can be made in terms of the content of imagery/hallucinations, which can either be composed of elementary or complex visual features.

2.2.2 Elementary Imagery and Hallucinations

Elementary imagery and hallucinations comprise visual experiences ranging from single-light flashes (known as phosphenes) to more repetitive visual elements with distinct boundaries, and then on to complete geometric images. Light flashes typically occur as single elements in the earliest stages of hallucinogen intoxication, while in later stages, the various elements multiply and may form more discrete boundaries (Shanon 2002). However, the most elaborated elementary hallucinations correspond to visions of geometrical figures, described by the intoxicated subject with words such as transparent oriental rug, wallpaper design, filigreed object of art, cobweb-like figure, spiral and prism. These elementary hallucinations are highly typical for serotonergic hallucinogens, and have been documented since the late eighteenth century (Lewin 1886; Mitchell 1896; Mooney 1896; Prentiss and Morgan 1896).

The first systematic analysis of hallucinogen-induced geometrical images was conducted by Heinrich Klüver by administrating mescaline-containing peyote cacti to several subjects, including himself (Klüver 1928, 1942). Despite large inter- and intra-individual differences in the descriptions of the ensuing geometric figures, recurring patterns with a remarkable uniformity were seen across subjects (Fig. 1). Klüver called these patterns "form constants" and categorized them into four classes, as follows: (1) lattices (including gratings, fretworks, honeycombs, filigrees, and chessboard designs), (2) cobwebs, (3) tunnels (including alleys, funnels, cones and vessels), and (4) spirals.

Almost five decades later, Siegel and coworkers assessed the consistency of this categorization scheme across different psychedelic substances in a study employing European subjects (Siegel and Jarvik 1975). To this end, four of the subjects included in the study were trained to categorize their visual experiences by repeated presentation of example visual stimuli for each of the four Klüver form constants (lattices, cobwebs, tunnels and spirals), as well as four additional investigator-defined categories. Furthermore, the four subjects were trained to categorize eight different groupings of color, movement and action patterns. The subjects then received either LSD (50 and 100 μg), 2-bromo-LSD (also known as BOL; 50 and 100 μg), psilocybin (10 and 20 mg), mescaline (200 and 300 mg), delta-9-tetrahydrocannabinol (THC) (10 and 20 mg), phenobarbital (30 and 60 mg), or D-amphetamine (5 and 15 mg) in a series of single-blind weekly test sessions. Consequently, they continually reported their eyes-open visual experiences in a completely dark chamber.

Interestingly, classical hallucinogens, including psilocybin, mescaline and LSD, frequently induced form constants of the lattice and tunnel types. Furthermore, hallucinogen-induced visual experiences were dominated by red, orange, or yellow colors, while blue colors were most commonly observed after the administration of delta-9-THC. Lastly, explosive and/or rotational motions were most frequently reported after the administration of classical hallucinogens, followed by pulsating motions. Thus, visual experiences showed marked consistency across various

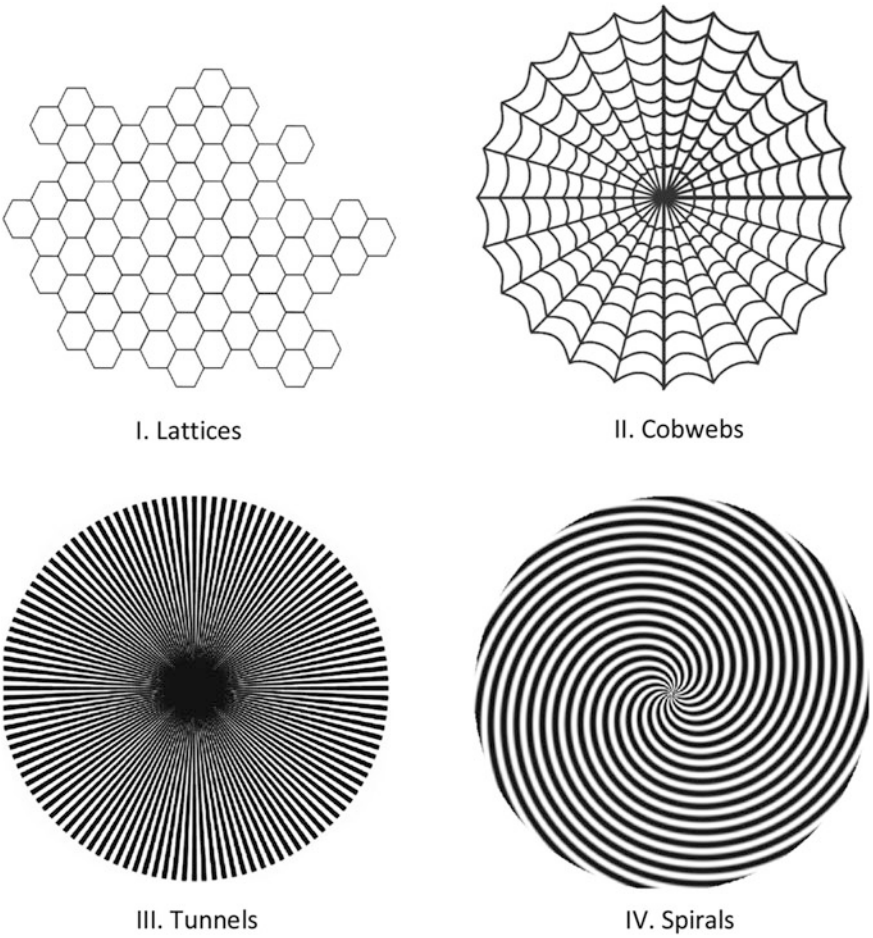

Fig. 1 Sample stimuli for the four hallucinatory form constants: (*I*) lattices (including gratings, fretworks, honeycombs, filigrees, and chessboard designs), (*II*) cobwebs, (*III*) tunnels (including alleys, funnels, cones, and vessels) and (*IV*) spirals.

classical hallucinogens, not only in terms of specific form constants, but also in terms of the color and movement categories.

Siegel went on to explore whether these consistencies in form, movement, and color are consistent across different cultures. Intriguingly, tunnels and funnels have been habitually reported by curanderos (folks healers or shamans) when using ayahuasca in medical and spiritual rites (Naranjo 1973). Furthermore, Tukano Indians in the Amazon region of Colombia often decorate their homes and pottery with geometrical paintings of images seen during ayahuasca rituals, including

curves, spirals, lattices, and the sun (Reichel-Dolmatoff 1972). To further test the concept of cultural consistency, Siegel and colleagues conducted a small study in Mexico with four male Huichols, who ingested the equivalent of ~200 mg of mescaline in the form of a peyote button suspension during a traditional ceremony (Siegel and Jarvik 1975). Four hours after ingestion, the subjects made a total of 68 reports about simple forms, colors, and movement patterns, and a total of 27 reports referring to complex scenes. The predominant reported form was a lattice tunnel, and the predominant perceived movement was an explosive motion toward the subjects. These observations provide support for the hypothesis of a cross-cultural consistency of elementary hallucinations. However, blue was more often experienced by the Huichols than by the four European subjects who received mescaline in the tests described above.

2.2.3 Complex Imagery and Hallucinations

Complex imagery and hallucinations include on the one hand visual images of people, animals, or entities, and on the other hand, visions of whole scenes and landscapes. Hence, these hallucinations are usually composed of non-repetitive, figurative visual features, and they transport more semantic content than elementary hallucinations. Complex hallucinations are not reported as frequently as elementary hallucinations (Studerus et al. 2011; Kometer et al. 2012, 2013), and some people never seem to experience complex hallucinations following hallucinogenic drug administration (Shanon 2002).

Complex hallucinations usually appear after the first elementary hallucinations are observed (Butterworth 1967; Siegel and Jarvik 1975), and they are regarded in the shamanic tradition as higher stages of visioning (Reichel-Dolmatoff 1975; Lewis-Williams et al. 1988). At low drug doses, complex hallucinations only occur in the closed-eyes state or in complete darkness. However, with increasing drug doses, they are first seen with opened eyes in a dimmed environment or at the periphery of the visual field (Siegel and Jarvik 1975). At high drug doses and particularly with DMT, complex hallucinations are also observed with fully opened eyes in an undimmed environment (Shanon 2002; Cott and Rock 2008). Indeed, under these conditions, the subject fails to experience a strong distinction between the eyes-open and eyes-closed states, but most subjects nevertheless prefer to close their eyes to prevent external stimuli-mediated interruptions of internally driven percepts (Shanon 2002). Furthermore, at higher drug doses, complex hallucinations are increasingly experienced as having strong prevalence and independence. This phenomenon seems especially pronounced with DMT (Luke 2011).

The content of complex hallucinations is far-reaching and can largely differ between and within subjects. The scenes perceived under the influence of serotonergic hallucinogens encompass all-inclusive, progressively developing, visualized scenarios, varying from brief glimpses and snapshots to full-fledged panoramas viewed as in a film or theater (Shanon 2002). For instance, subjects have described incredible and beautiful landscapes, as well as futuristic cities (Shanon 2002). The

visual images seen in the hallucinogen-induced states can include objects, people, human faces, and animals encountered in the visual environment, such as the anaconda or jaguar (Reichel-Dolmatoff 1972, 1975; Siegel and Jarvik 1975). Interestingly, these animals are a common aspect of ayahuasca-induced visions in shamanic rituals (Reichel-Dolmatoff 1972, 1975; Winkelman 2002), perhaps because certain animals have a special meaning for the affected individuals within daily life and during healing rituals (Harner et al. 1990; Saunders 1994; Winkelman 2002; Shepard 2004).

2.3 *Audiovisual Synesthesia*

Visual percepts observed in the hallucinogen-induced state can also be driven by stimulation of nonvisual sensory modalities a phenomenon termed synesthesia (Ellis 1898; Klüver 1966; Dittrich 1998; Shanon 2002; Studerus et al. 2011; Kometer et al. 2012; Brogaard 2013; Kometer et al. 2013; Luke and Terhune 2013). Most often, these visual percepts are modulated by auditory stimuli, such as the sound of music (Studerus et al. 2011; Luke and Terhune 2013). Only rarely are they reported to be induced by haptic, kinesthetic, or algesic stimuli (Klüver 1966; Luke and Terhune 2013). In agreement with these observations, intensified experiences of color and brightness were documented in an early study during the presentation of auditory tones before versus after drug administration (Hartman and Hollister 1963). However, early behavioral studies often suffered from methodological problems, including lack of a placebo control, absence of a double-blind design, and a lack of randomized group assignments. Accordingly, further studies are required to assess the capacity of hallucinogens to induce synesthesia in more detail.

2.4 *The Role of the Self in Visual Experiences*

Hallucinogen-induced visual experiences are frequently described as having a deeply amended and personalized meaning for the subject, with profound individual significance (Dittrich 1998; Shanon 2002; Díaz 2010; Shanon 2010; Studerus et al. 2011; Froese et al. 2013). As described previously, the visual landscape may look new, and everything might seem as if it were viewed for the first time (Díaz 2010). Therefore, serotonergic hallucinogens change not only the visual percept per se, but also the unique relationship between the viewer and the visual percept. In line with this view, complex visual imagery and hallucinations can stem from autobiographic memory (Studerus et al. 2011) or can be characterized by a special psychological relationship to the current life situation of the subject (Shanon 2002). Hence, the appearance of visual hallucinations is strongly linked to the emotional state of the subject at the time of drug administration and

thereby provide significant for the subject. Not rarely, visual hallucinations are described as exceedingly beautiful, surpassing anything ever seen, dreamt, or imagined (Shanon 2002). Such affirmative experiences are usually connected with intense positive emotions, while an anxious ego dissolution might be visualized by the subject in terms of terrifying images or scenarios. The strong association between autobiographic memory, emotions, and visual imagery/hallucinations has been exploited in psycholytic or psychedelic therapy, because this association provides a way to access and transform autobiographic memories and emotions (Leuner 1967; Grof 1973; Grinspoon and Bakalar 1986; Vollenweider and Kometer 2010; Carhart-Harris et al. 2012).

3 Neuropsychopharmacological Mechanisms

Serotonergic hallucinogens provoke a wide assortment of visual phenomena, suggesting that one single neuropsychopharmacological mechanism is unlikely to explain such vast phenomenological diversity. In this section, several partially overlapping, potential mechanisms of hallucinogen action will be discussed, ranging from mechanisms that act at the cellular level to mechanisms that act at the whole-brain level. Given that only a limited number of studies have specifically addressed the neural mechanisms underlying serotonergic drug-induced visual hallucinations, we will also consider the experimental evidence linking these mechanisms with the formation of visual perceptual alterations under various psychiatric conditions and during neurological disease states.

3.1 Primary Pharmacological Mechanism: 5-HT2A Receptor Activation

Serotonergic hallucinogens (e.g., psilocybin) display agonistic activity at several serotonergic receptors, including serotonin 5-HT2A, 5-HT2C, 5-HT1A, and 5-HT7 receptors (Nichols 2004; Sard et al. 2005; Ray 2010). However, the activation of 5-HT2A receptors seems to be primarily responsible for the psychedelic effects of these agents (Nichols 2004; Vollenweider and Kometer 2010). Early support for this view is provided by animal studies demonstrating that discriminative stimulatory hallucinogenic actions correlate with drug affinity at the 5-HT2A receptor (Glennon et al. 1983, 1984, Sanders-Bush et al. 1988). Furthermore, these actions can be blocked by the preferential 5-HT2A antagonists, ketanserin, and pirenperon (Colpaert et al. 1982; Leysen et al. 1982; Colpaert and Janssen 1983). More recently, hallucinogen-induced head shaking was used as an animal model of psychedelic drug action, and was found to be absent in transgenic mice lacking

5-HT2A receptors (González-Maeso et al. 2007) and in rats after administration of the 5-HT2A receptor antagonist M100907 (Schreiber et al. 1995).

In agreement with the crucial role of 5-HT2A receptors in serotonergic hallucinogen mechanisms of action, several investigations established that ketanserin can almost completely block the subjective psychedelic effects of psilocybin in humans (Vollenweider et al. 1998; Carter et al. 2005; Kometer et al. 2011; Quednow et al. 2012). These effects include elementary and complex hallucinations, audiovisual synesthesia and the altered significance of visual percepts (Kometer et al. 2012, 2013). Furthermore, the psilocybin-induced decrease in the visual evoked N170 potential, a marker of psilocybin-induced visual hallucinogenic activity in humans (discussed below) (Kometer et al. 2011, 2013), was also blocked by the administration of ketanserin (Kometer et al. 2013).

3.2 *From 5-HT2A Receptor Activation to Increased Excitation*

Activation of 5-HT2A receptors by serotonergic hallucinogens induces a robust increase in excitatory postsynaptic currents (EPSCs) of pyramidal neurons, predominantly within layer 5 of the frontal cortical area (Aghajanian and Marek 1997; Béïque et al. 2007; González-Maeso et al. 2007, 2008; Riga et al. 2014) and occipital cortex (Moreau et al. 2010). By contrast, inhibitory postsynaptic currents (IPSCs) are only weakly increased (Riga et al. 2014). The overall increase in excitation is abolished not only by administration of specific 5-HT2A receptor antagonists (Aghajanian and Marek 1997), but also by administration of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists (Aghajanian and Marek 1997; Zhang and Marek 2008), metabotropic glutamate receptor (mGluR) agonists (Aghajanian and Marek 1997) and positive allosteric modulators of mGluR2 (Benneyworth et al. 2007). Taken together, these observations indicate that glutamatergic activity downstream of 5-HT2A receptor activation is strongly implicated in the mechanism of action of serotonergic hallucinogens. In keeping with this view, stimulation of postsynaptic 5-HT2A receptors on a subpopulation of glutamatergic cells in deep cortical layers increased glutamatergic recurrent network activity, resulting in an augmentation of EPSCs, mainly in layer V (Béïque et al. 2007; Aghajanian 2009; Moreau et al. 2010). Although the link between 5-HT2A receptor activation and increased excitation has been investigated in detail, the relationship between excitation and visual hallucinations has rarely been experimental investigated and will therefore be discussed by taking stimulation experiments and computational models into account.

3.3 *From Increased Excitation to the Formation of Visual Hallucinations*

3.3.1 Increased Excitation and Visual Hallucinations in Stimulation Experiments

The idea that increased excitation of cortical visual areas could lead to the formation of visual hallucinations derived in the nineteenth century from the observations that electrical stimulation of cortical areas in humans can induce several visual phenomena. Specifically, researchers observed that hallucinations of meaningful images were induced in some patients with epilepsies (Penfield and Rasmussen 1950; Penfield and Jasper 1954; Horowitz and Adams 1970) or schizophrenia (Ishibashi et al. 1964) by directly stimulating the temporal lobe. The content of these electrical-induced hallucinations seems to be related to what patients experienced immediate before surgery (Mahl et al. 1964). Furthermore, researchers found that visual phosphene, characterized by rather shapeless, nonspecific impressions of light, were induced by applying rectangular electric pulses to large electrodes placed on the cortical surface (Knoll 1958; Knoll et al. 1962a, b, 1963) or by applying magnetic fields (Thompson 1910; Dunlap 1911; Magnusson and Stevens 1911; Barlow et al. 1947; Seidel 1968). Since these early findings, it has been hypothesized than an increase in electrical or chemical processes underlies the formation of hallucinations and phosphenes.

More recent studies using electrical stimulation (Lee et al. 2000; Murphey et al. 2009; Jonas et al. 2013) or transcranial magnetic stimulation (TMS) (Hallett 2000; Kammer et al. 2001; Stewart et al. 2001) mostly confirm these early findings and extend them in several important ways. In TMS studies, it was found that phosphenes can be reliably induced by a certain stimulation protocol and head positioning (Hallett 2000; Kammer et al. 2001; Stewart et al. 2001). The threshold for experiencing these phosphenes differ between subjects and has even been taken as a marker for visual cortical excitability (Boroojerdi et al. 2000; Oliveri and Calvo 2003; Taylor et al. 2011). Interestingly, in subjects experiencing hallucinations this threshold was found to be decreased compared to non-hallucinators (Aurora et al. 1998, 2003; Taylor et al. 2011), providing further evidence that an increase in excitability underlies the formation of visual hallucination.

Electrical stimulation studies using modern tools to guide stimulation in various occipital, temporal, and parietal areas mostly found that the complexity of the visual phenomena tended to increase along the posterior–anterior axis (Lee et al. 2000; Jonas et al. 2013), however see also (Murphey et al. 2009). In addition, the probability of evoking visual phenomena was found to be generally higher in the right compared to the left hemisphere (Jonas et al. 2013). These anatomical observations are in line with the fMRI and leson studies suggesting that brain areas along the occipito-temporal cortex are hierarchically organized for processing increasingly complex visual features (Grill-Spector and Malach 2004). Thus, according to these findings, the content of the hallucinatory experience is to some

extend driven by the cortical location of increased excitation. However, this association may not be strict because this association was not always found in stimulation studies (Murphey et al. 2009) and because each visual area is highly connected with areas providing top-down or bottom-up input (Grill-Spector and Malach 2004).

3.3.2 Increased Self-organized Excitation in Computational Models of Visual Hallucinations

Since the 1970s, a number of computational models have been proposed to explain how increased excitation leads to the formation of elementary, geometric hallucinations (Ermentrout and Cowan 1979; Bressloff et al. 2001, 2002; Gutkin et al. 2003; Rule et al. 2011; Billock and Tsou 2012; Butler et al. 2012). All these models are to some extent based on the idea of the Turing mechanism (Turing 1952), which explains morphogenesis, i.e., pattern formation during biological development, by reaction-diffusion systems. The idea of the turning mechanism has been transposed to the functioning of the brain in the Wilson–Cowan neural network equation (Wilson and Cowan 1973) and was fist applied to explain elementary geometrical hallucinations by Ermentrout and Cowan (Ermentrout and Cowan 1979). Specifically, they postulated a two-layer neural network model of excitatory and inhibitory neurons in primary visual cortex (V1). Similarly to the turing mechanism, this model contains two main elements that explain the formation of visual hallucinations: first, an asymmetry between two interacting mechanisms (excitation and inhibition) and second, a diffusion-like mechanism for spreading their influence. Within this model, a hallucinogen-induced increase in excitation destabilizes the resting state because of a distributional asymmetry between inhibition and excitation. As a consequence, spontaneous spatiotemporal patterns of activity emerge due to spreading of negative feedback by lateral interactions. These spatiotemporal patterns can be viewed as a self-organization process to reintroduce stability. In order to see what subjects would visually experience due to the emergent spatiotemporal patterns, a retinocortical mapping was applied, allowing neuronal activity in V1 to be transformed into retinal coordinates. Thus, the retinocortical mapping makes it possible to define the retinal input that would be required to induce these spatiotemporal patterns. Using this model Ermentrout and Cowan (1979) found that several patterns could be induced that resemble the form constant described by Klüver. This model did particularly well describing lattice patterns (Fig. 1), which are frequently induced by serotonergic hallucinogens.

Although this initial model was innovative, inspiring and influential, it was not able to produce all form constants and a large drawback was that it was not based on the actual neural architecture of the visual cortex. To overcome these problems, several authors (Bressloff et al. 2001, 2002; Butler et al. 2012) proposed models to explain geometrical elementary hallucinations based on the structure of V1. The model of Bressloff and colleagues incorporated the findings of anatomical and functional studies that the detection of local contours and oriented edges in visual

input is mediated by structured connections between subgroups of V1 neurons that are organized in hypercolumns. This pattern of structural organization, combined with the neuronal Turing mechanism and increased cortical excitation, was able to generate form constants. Specifically, this model was able to describe some of the more complicated form constants, including cobwebs, honeycombs, and lattice (Bressloff et al. 2001, 2002).

Together, these mathematical models provide an appealing explanation for why increased excitation in V1 leads to the formation of specific elementary geometrical hallucinations. In line with these models, relatively simple visual features such as lines can be processed only within V1 (Grill-Spector and Malach 2004) and therefore V1 activity may be sufficient to explain form constants comprised of lines, such as lattices patterns. However, certain elementary form constants, as well as complex hallucinations, remain unexplained by these models and seem to require models incorporating higher level visual areas. Higher cortical areas may further be required to explain why these hallucinogen-induced experiences are often experienced as being meaningful (Froese et al. 2013), beautiful and detailed and why the interindividual predisposition for experiencing these visual hallucinations is associated with the personality trait absorption (Studerus et al. 2012). Thus, additional models incorporating higher level visual areas are required to explain, how increased self-organized excitation can explain a larger phenomenological range of serotonin hallucinogen-induced visual perceptual alterations. In the next section, alpha oscillations will be discussed as a systemic mechanism for regulating excitation across low- and high-level cortical visual areas, which could potentially be implicated in the formation of different type of visual perceptual alterations and hallucination.

3.3.3 Alpha Oscillations: Increased Spontaneous Excitation that Overwhelms Stimulus-Induced Excitability

Parieto-occipital alpha oscillations (8–12 Hz) regulate trough inhibition the excitability levels of neurons across the whole cortical visual system and thereby strongly influence visual perception (Foxe et al. 1998; Thut et al. 2006; Klimesch et al. 2007; Rihs et al. 2007; Romei et al. 2008a, b; Busch et al. 2009; Jensen and Mazaheri 2010; Romei et al. 2010; Klimesch 2011; Mathewson et al. 2011; Jensen et al. 2012). In line with this view, decreased alpha power levels were for instance found to be associated with increased neuronal firing rates (Haegens et al. 2011) and with a decreased threshold for perceiving visual stimuli (Ergenoglu et al. 2004; Thut et al. 2006; Hanslmayr et al. 2007; van Dijk et al. 2008) and TMS-induced phosphenes (Romei et al. 2008a, 2010). Furthermore, the likelihood of perceiving subliminal visual stimuli rhythmically varies with the phase of alpha oscillations (Busch et al. 2009; Spaak et al. 2014; VanRullen et al. 2014). Given this crucial role of alpha oscillations in modulating excitability through inhibition across cortical visual systems, a hallucinogen-induced decrease in alpha oscillations may not only be in line with the increased cortical excitation found in animals (Moreau et al.

2010), but may additionally explain a wide range of hallucinogen-induced phenomenology.

To address this idea, we recently assessed in healthy human subjects the effect of psilocybin (215 μg/kg vs. placebo) on posterior parieto-occipital alpha oscillations observed before and during presentation of simple visual stimuli (Kometer et al. 2013). A high level of parieto-occipital alpha power was seen in the placebo condition before the presentation of the stimuli, thus in the absence of any task-relevant visual input. This indicates a high level of inhibition reduces the excitability of the visual pathways in the absence of task-relevant visual input (Klimesch 2011; Palva and Palva 2011). Psilocybin strongly attenuated this high level of alpha power, suggesting that psilocybin increases the excitability of the visual pathway in the absence of externally presented stimuli. Thereby, spontaneous self-organized activity may gain perceptual quality, which could form the base for psilocybin-induced visual hallucinations. In line with this view, spontaneous self-organized background activity was found to resemble the neuronal activity seen by presenting simple visual geometric (Kenet et al. 2003). Therefore, it has been postulated that a inhibitory mechanism is necessary to prevent that the usually subliminal spontaneous neuronal activity leads to conscious percepts in the form of elementary visual hallucinations (Billock and Tsou 2007). Alpha oscillation may constitute this inhibitory mechanism, which was found to be attenuated by psilocybin, possible leading to a conscious perception of spontaneous neuronal activity in the form of hallucinations (Kometer et al. 2013).

Interestingly, alpha oscillations are not only implicated in regulating spontaneous internal-driven excitability, but also in controlling stimulus-induced excitation (Hanslmayr et al. 2009; Klimesch 2011). This leads to the question of whether the increased excitability seen in the absence of task-relevant input influences the excitation that is induced by the presentation of external visual stimuli? Such a stimulus-induced increase in excitation is seen by the strong decrease in alpha power around 200–400 ms after the presentation of the stimuli (Hanslmayr et al. 2009; Klimesch 2011). Interestingly, psilocybin was found to block this stimulus-induced reduction of alpha power (Kometer et al. 2013) and the lack of stimulus-induced alpha power reduction was further found to be due to the already attenuated prestimulus alpha power level (Kometer et al. 2013). Thus, by decreasing prestimulus alpha power, psilocybin seems to induce a dysbalance between the excitability that is seen in the absence of external visual input and the excitability that is induced by the presentation of the stimulus. Thus, psilocybin induces a processing mode, in which stimulus-driven cortical excitation is overwhelmed by spontaneous self-organizing neuronal excitation (Kometer et al. 2013). This psilocybin-induced shift away from stimulus-driven information processing toward internal-driven processing could well contribute to the formation of hallucinations, given the longstanding proposal that increased internal-driven information processing may lead to the formation of visual hallucinations (Horowitz 1975; Allen et al. 2008). Interestingly, a similar bias toward internal-driven information processing is seen at the single cell level. Specifically, the activation of 5-HT2A receptors was found to have an opposite effect on low and high neuronal firing rates

(Watakabe et al. 2009). That is, 5-HT2A receptor activation suppresses the activity of neurons with high firing rates (Watakabe et al. 2009), which are usually induced by external visual stimuli (Quiroga et al. 2005; Montemurro et al. 2008). By contrast, low firing rates, which may constitute stimulus-independent, internal-driven background activity, were found to be facilitated by 5-HT2A receptor activation (Watakabe et al. 2009). Thus, in line with our finding stimulus-independent background activity may overwhelm stimulus-induced processing. However, the strong effect of psilocybin on alpha oscillations may not only be implicated in the formation of visual hallucinations, but may further underlie a psilocybin-induced increase in distractibility (Carter et al. 2005) or decrease in working memory (Wittmann et al. 2007) due to the crucial role of alpha oscillations in dynamically adjusting spatial and temporal excitability parameters for optimizing processing for task demands (Capotosto et al. 2009; Zanto et al. 2011; Bonnefond and Jensen 2012; Hsu et al. 2014; Zumer et al. 2014). For instance, psilocybin may disrupt the possibility of increasing alpha oscillations in anticipation of distracting stimuli, which was found to be required to prevent interference of distracters with working memory maintenance (Bonnefond and Jensen 2012). Hence, taken together the decrease in alpha oscillations seems to amplify internal-driven excitation that overwhelms stimulus-induced excitations and in addition may induce cognitive impairments such as increased distractibility.

3.4 Dysbalance Between Early Low-Level and Late High-Level Visual Processing

3.4.1 Evidence from Phenomenological and Behavioral Studies

Converging lines of evidence form phenomenological and behavioral suggest that serotonergic hallucinogens differently modulate early low-level visual processing and late high-level visual processing. Specifically, phenomenological studies indicate that the perception of elementary visual features such as the brightness, the local contrast and the saturation of colors is subjectively increased by hallucinogens (Klüver 1942; Rümmele and Gnirss 1961; Klüver 1966; Dittrich 1998; Díaz 2010). These elementary visual features are typically processed fast (Proverbio and Zani 2002) and within low-level visual areas (Grill-Spector and Malach 2004). By contrast, the perception of whole objects, the construction of the visual space, and the detection of global motion patterns, which all require more time (Johnson and Olshausen 2003) and higher level visual areas (Grill-Spector and Malach 2004) to be processed, seems to be impaired by hallucinogens (Hill et al. 1968; Fischer et al. 1970; Hill and Fischer 1973; Dittrich 1998; Carter et al. 2004; Díaz 2010). Together, these findings suggest that hallucinogens impair late high-level processing, while increasing or having no effect on early low-level processing. In the following section, we will present studies that address this hypothesis in more detail

by using high-density EEG recordings to assess the spatiotemporal dynamic of visual processing in psilocybin-induced states.

3.4.2 P1 Amplitude and V1 Activity: Increased Early Low-Level Processing

Using high-density EEG recordings psilocybin was found to dose-dependently increase the amplitude of the early visual evoked P1 potential selectively over the medial occipital electrode sites (Kometer et al. 2011, 2013). This psilocybin-induce increase, which was seen 100 ms after the presentation of simple visual stimuli was found by mathematical source reconstruction techniques to reflect increased activity in early visual area V1 (Kometer et al. 2011). Because processing of brightness has been associated with the medial P1 potential (Proverbio and Zani 2002) and with activity in V1 (Salminen-Vaparanta et al. 2013), this psilocybin-induced increase in the medial P1 potential may be the neuronal correlate of the often reported hallucinogen-induced increase in brightness perception (Kometer et al. 2011). Interestingly, this medial P1 increase induced by psilocybin was found to be driven by the hallucinogen-induced decrease in prestimulus alpha oscillations (Kometer et al. 2013). This suggests that the psilocybin-induced increase in visual cortical excitability before the presentation of the visual stimulus may have amplified the processing elementary visual features, such as the brightness, in early visual areas.

3.4.3 N170 Amplitude and Extrastriate Activity: Decreased Global Integration

In contrast to this initial increase in early visual cortex activity, during a later time frame ($\sim$150–190 ms after stimulus presentation) psilocybin dose-dependently decreased the visual N170 potential to the same simple visual stimuli (Kometer et al. 2011, 2013). This psilocybin-induced decrease of the N170 amplitude was localized in the lateral occipital complex (LOC) and the fusiform gyrus, which both belong to extrastriate, higher visual areas. Thus, this psilocybin-induced decrease of the N170 decrease is in line with the hypothesis that hallucinogens disrupt late higher level visual processing.

More specifically, the N170 potential has been implicated in global integrative processes, such as the structural encoding of emotional face expressions (Rossion et al. 2000; Bernasconi et al. 2013; Schmidt et al. 2013) or object recognition (Murray et al. 2002; Kometer et al. 2011, 2013; Knebel and Murray 2012). For instance, the N170 potential has been found to be crucial for object completion, which is the process of integrating local information into complex object representation and of interpolating missing parts of objects. This process is required due to the ambiguous and incomplete retinal information under partial occlusion or poor illumination conditions. In support of the proposed role of the N170 potential in object completion, the N170 potential was found to be higher for incomplete,

Kanizsa figures, compared to control figures (Murray et al. 2002, 2006; Kometer et al. 2011, 2013; Knebel and Murray 2012).

Using these Kanizsa figures, we found that psilocybin induced a more pronounced reduction of the N170 amplitude and activation of the LOC in response to Kanizsa figures compared to control figures (Kometer et al. 2011, 2013) (Fig. 2a). This indicates that psilocybin disrupts the neuronal processes of object completion. Given that object completion is crucial for perceiving coherent and meaningful structures in natural images (Lesher 1995), this disruption in object completion is likely to contribute to psilocybin-induced alterations in visual perceptual experiences. Interestingly, this contribution may be seen in the observation that subjective visual perceptual alterations first appear in dimmed environment (Siegel and Jarvik 1975); thus in lighting situations that require extensive object completion.

Most direct support for the view that the N170 potential decrease is associated with visual alterations derives from the finding that the reported intensity of subjective visual hallucinations correlated with decreases in the N170 amplitude in both the Kanizsa and the control conditions (Kometer et al. 2011, 2013). This association was equally seen for elementary and complex hallucinations, as well as audiovisual synethesia (Kometer et al. 2013) (Fig. 2c). Exploring this relationship in more detailed using mathematical source reconstruction techniques indicated that the psilocybin-induced decrease in the right-lateralized LOC and posterior parietal areas during the time frame of the N170 potential most strongly correlated with the intensity of visual perceptual alteration (Kometer et al. 2011) (Fig. 2b). This localization is in accord with the results of previous brain imaging studies reporting decrease extrastriate activation in response to external visual stimuli in hallucinating patients compared to patients without hallucinations (Howard et al. 1995; Ffytche et al. 1998; Oertel et al. 2007). Furthermore, decreased activation during the time frame of the N1/N170 potential has been associated in patient studies with the formation of visual (Spencer et al. 2004) and acoustic hallucinations (Tiihonen et al. 1992; Hubl et al. 2007). This strong association between the N1/N170 potential and hallucinations seems to be driven by the crucial role of this potential in global integration processes that are required to perceive coherent and meaningful structures in sensory input. Global integration is further important to differentiate internal-driven and external-driven sensory percepts, a process that is associated with the N1 potential (Ford et al. 2007; Heinks-Maldonado et al. 2007; Gentsch and Schütz-Bosbach 2011; Ford et al. 2013; Hubl et al. 2014). Taken together, the decrease of N170 potential by hallucinogens is a key mechanism underlying the formation of visual hallucinations due to the role of the N170 potential in global integration required for recognizing the meaning and the self-reference of visual percepts.

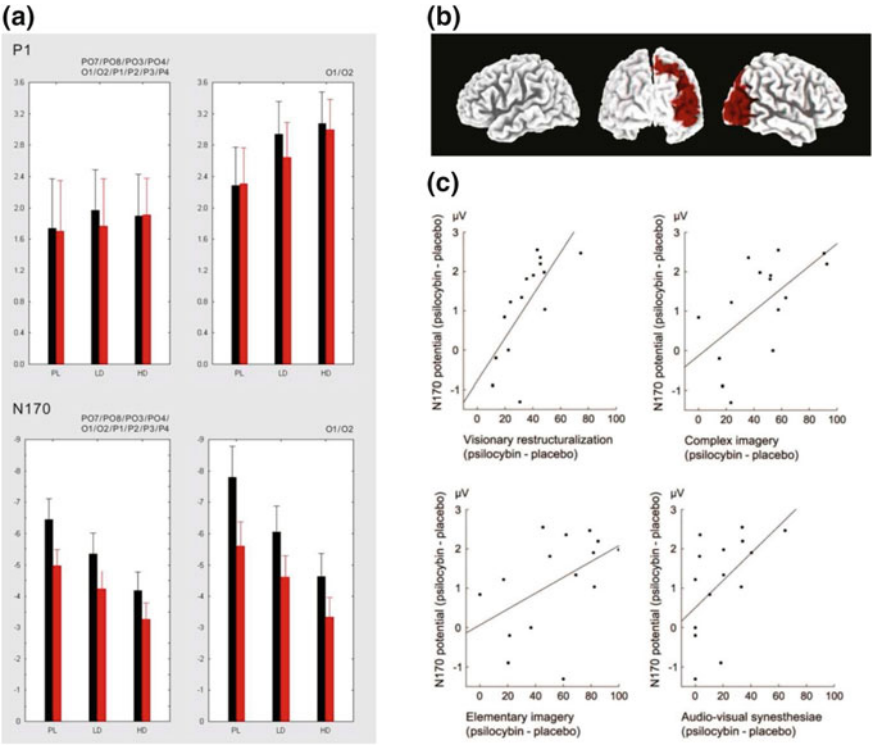

Fig. 2 **a** The bar graphs display the effect of placebo (PL), a low dose (LD) and a high dose (HD) of psilocybin on the amplitude of the P1 and N170 potential to kanizsa (*black*) and non-kanizsa figures (*red*) measured from 10 parieto-occipital electrodes sites (*left bar graphs*) and from the medial occipital electrode sides O1/O2 (*right bar graphs*) **b** *Red areas* display the psilocybin-induced decreases in current source density during the time period of the N170 potential that positively correlated with the intensity of psilocybin-induced visual hallucinations. [Figures 2a and 2b are reprinted from Kometer et al., The 5-HT2A/1A Agonist Psilocybin Disrupts Modal Object Completion Associated with Visual Hallucinations, page 399–406, Biological Psychiatry, Copyright (2011), with permission from Elsevier]. **c** The psilocybin-induced decrease of the N170 amplitude significantly correlates with the psilocybin-induced increase in visual restructuralization, complex imagery, elementary imagery and audiovisual synesthesiae as measured by the 5D-ASC questionnaire [Reprinted from Kometer et al., Activation of Serotonin 2A Receptors Underlies the Psilocybin-Induced Effects on α Oscillations, N170 Visual-Evoked Potentials, and Visual Hallucinations, page 10544–10551, The Journal of Neuroscience, Copyright (2013), with permission from Society for Neuroscience]

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