Psilocybin, LSD, Mescaline and Drug-Induced Synesthesia

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Penultimate draft. Please do not quote.

Abstract

Studies have shown that both serotonin and glutamate receptor systems play a crucial role in the mechanisms underlying drug-induced synesthesia. The specific nature of these mechanisms, however, continues to remain elusive. Here we propose two distinct hypotheses for how synesthesia triggered by hallucinogens in the serotonin-agonist family may occur. One hypothesis is that the drug-induced destabilization of thalamic projections via GABAergic neuronal circuits from sensory areas leads to a disruption of low-level, spontaneous integration of multisensory stimuli. This sort of integration regularly occurs when spatial and temporal attributes match. Destabilization of feedback loops, however, can result in incongruent experiences or binding of random thalamus activation with sensory input in a particular sensory modality. The second hypothesis builds on embodied cognition, cases in which visual images of external stimuli activate task-related neural regions. On this proposal, binding processes that do not normally generate awareness become accessible to consciousness as a result of decreased attentional discrimination among incoming stimuli.

Keywords:

5-HT2A serotonin receptors; anxiety disorder; attentional discrimination; drug-induced hallucinations; drug-induced synesthesia; embodied cognition; glutamate-receptor system; hallucinogens; LSD; mescaline; psychedelics; psilocybin; sensory modality; serotonin agonist; depression

List of abbreviations

HPPD: hallucinogen-persisting perceptual disorder associated with the abuse of hallucinogenic substances.

5-HT2A: 5-hydroxytryptamine 2A subtype of the 15 different serotonin receptors.

***Gamma*-Aminobutyric Acid** (**GABA):** the key inhibitory neurotransmitter in the mammalian central nervous system playing the principal role in reducing neuronal excitability throughout the nervous system.

1. Introduction

Synesthesia typically involves either the stimulation of one sensory modality giving rise to an experience in a distinct sensory modality (such as when a smell or taste gives rise to a color experience) or the stimulation of a single sensory modality giving rise to an unusual qualitative experience (such as when an achromatic grapheme appears colored) (Baron-Cohen et al., 1987; Cytowic, 1989; Rich & Mattingley, 2002; Sagiv, 2005; Day, 2005; Sagiv & Ward, 2006; Brogaard, 2012). More generally, synesthesia involves an aberrant binding of features from different sensory or cognitive streams that are associated with atypical conscious experiences or thoughts.

The trigger of a synesthetic experience, say, a grapheme or a sound, is normally referred to as *the inducer* while the experience to which the inducer gives rise, say, the synesthetic color associated with a grapheme or a sound, is normally referred to as *the concurrent* (Grossenbacher & Lovelace, 2001). There is extensive variability in the inducer-concurrent pairs among synesthetes. Some synesthetes experience interactions between taste or smell and vision reporting, for example, that the taste of beef is dark blue or that the smell of almonds is pale orange (Day, 2005; Dixon et al., 2004). Others experience interactions between music and smell or color reporting, for example, that they are smelling music or experiencing a French tenor's voice as being simultaneously red and green (Ramachandran et al., 2005). Sometimes context also affects the nature of the inducer-concurrent pair. For example, Blake et al. (2005) found that subjects described the same grapheme as having different synesthetic colors when viewed amidst letters and when viewed amidst numbers (see **Fig. 1**).

Three main types of synesthesia have been identified (Grossenbacher & Lovelace, 2001). The most common of them is *developmental or genuine synesthesia*. This condition reportedly develops at birth or in early childhood (Hubbard, 2007); it tends to be hereditary (Baron-Cohen et al., 1996); and it remains relatively consistent (or enduring), and systematic (or non-random) as each inducer has a highly specific concurrent (Baron-Cohen et al., 1987; Mattingley et al., 2001; Ward & Simner, 2003; Simner et al, 2005; Simner et al., 2006; Ward et al., 2006; Cohen Kadosh et al., 2007).[1] For example, a 5-year old synesthete who experiences the number 3 as a particular shade of green will most likely continue to experience the number 3 as that particular shade of green for a considerable length of time (see **Fig. 2**).

[1] The Synesthesia Battery, an automated online test (available at www.synaesthete.org), allows for rigorous testing of both the tightness of the inducer and its concurrent and their stability and systematicity over time for the most common forms of developmental synesthesia (Eagleman et al., 2007).

In visual synesthesia, the concurrent can be either projected out into space (when, for example, the number 3, printed in black, looks green) or merely be associated with the inducer (when, for example, the number 3 is seen in the "mind's eye" as being dark blue or as having a detailed personality, as if it were a person) (Dixon et al., 2004; Smilek et al., 2007). The former condition is also known as projector synesthesia, whereas the latter is known as associator synesthesia.

Subjects with projector grapheme-color synesthesia tend to describe seeing the concurrent as positioned spatially in the same location as the inducing achromatic grapheme (and not simply as existing in their "mind's eye"). As a result, at least some grapheme-color synesthetes are subject to pop-out and grouping effects grounded in their concurrent synesthetic experiences (see **Fig. 3**). Pop-out effects allow synesthetes to identify graphemes in visual-search paradigms with far greater speed and accuracy than non-synesthetes (Ramachandran & Hubbard, 2001a, 2001b; Edquist et al*.,* 2006; Blake et al., 2005). For example, when an array of 2s that form a triangle are hidden within a field of distracter graphemes with incongruent synesthetic colors, the shape formed by the 2s may appear immediately and conspicuously, as if it were popping out of the array (see **Fig. 3**, box on the right) (Ramachandran & Hubbard, 2001b). For non-synesthetes, by contrast, the 2s and the distractor graphemes appear too homogenous for the triangle formed by the 2s to be immediately noticed (see **Fig. 3**, box on the left).

The second type of the condition is *acquired synesthesia*. This type has been reported to emerge after traumatic brain injury (Brogaard et al., 2012; Brogaard & Marlow, 2013), stroke (Ro et al., 2007; Beauchamp & Ro, 2008; Thomas-Anterion et al., 2010; Schott, 2012), seizures (Jacome & Gumnit, 1979), migraine (Alstadhaug & Benjaminsen, 2010), post-hypnotic suggestion (Cohen Kadosh et al., 2009), sensory substitution (Ward & Wright, 2014), and neuropathology involving the optic nerve and/or chiasm (Jacobs et al., 1981; Armel & Ramachandran, 1999; Afra et al., 2009). Like its developmental counterpart, the acquired form tends to be enduring and involuntary in the sense that synesthetes are unable to suppress the association between an inducer and its concurrent, although there are reports that the condition does not always persist (Jacome & Gumnit, 1979; Lessell & Cohen, 1979; Afra et al., 2009). Acquired synesthesia can be experientially indistinguishable from developmental synesthesia, although it is often simpler than its developmental counterpart, say, resembling light flashes (phosphenes) or pure color experiences (Afra et al., 2009). In some cases acquired synesthesia appears to be less inducer-specific than its developmental counterpart, meaning that the same concurrent may have several different inducers (Brogaard et al., 2012).

The third type, which is the main focus of this paper, is *drug-induced synesthesia*.[2] This condition tends to be experienced during exposure to hallucinogenic substances, such as psilocybin (which occurs naturally in some mushrooms, the most common of which are *Psilocybe cubensis*), lysergic acid diethylamide or LSD (which is a semi-synthetic hallucinogen derived from rye fungus), and mescaline (which occurs naturally in peyote cacti) (Shanon, 2002; Friedrichs, 2009; Sinke et al., 2012).[3] Hallucinogens (also known as psychedelics, psychotomimetics, or entheogens; see Ray 2010 for a survey of thirty five different hallucinogens) are psychoactive substances known to (dose-dependently) induce profound changes in perception, including changes in the experience of time or space, as well as alterations in moods, thoughts, and other mental states. LSD, the most potent of the three hallucinogens mentioned above, was found to have the highest correlation with visual disturbances compared to consciousness-altering substances such as amphetamines, cocaine, hypnosedatives, opiates, marijuana, and alcohol (Abrahams, 1983).

While some hallucinogens are artificially produced, others (for example, psilocybin and mescaline) occur naturally in plants. Plant-based hallucinogens have been used by early cultures, for example various groups of indigenous peoples native to the central or southern regions of Mexico, in a variety of sociocultural, medical, or ritual contexts (Stamets, 1996; Guzmán et al., 2000). Some hallucinogens have recently been found to produce mystical-type experiences marked by substantial and persisting personal meaning and spiritual significance, to which subjects attributed sustained positive changes in attitudes, moods, and behavior (Griffiths et al., 2006; Griffiths et al., 2008).

Drug-induced synesthesia tends to occur only during intoxication, although occasionally it can continue to occur for weeks or months after exposure (Abraham, 1983; Ffytche, 2007; Brogaard, 2013). This form of the condition is also involuntary but it has a much broader spectrum of inducers and concurrents as well as a greater intensity compared to developmental and acquired synesthesia (Hintzen & Passie, 2010). The visual disturbances of drug-induced synesthesia can give rise to some of the symptoms found in psychotic disorders such as schizophrenia (González-Maeso et al., 2008). Unlike subjects suffering from psychotic disorders, however, subjects who experience drug-induced synesthesia typically recognize the unreal nature of their visual disturbances (Hermle et al., 2012).

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[2] This paper pertains to studies of human subjects. However, Siegel and Jarvik (1975) describe animal (mice, pigeons, etc.) reactions to psychoactive drugs in general and hallucinogens in particular, but caution us that which behaviors support the notion of animals having hallucinations depends on the inferences we are willing to make about their behavior.

[3] Drug-induced synesthesia can be absent during intoxication. See Studerus et al., 2011.

Despite prodigious research on synesthesia, the mechanistic commonalities (if any) among the different types of synesthesia, the causes of the onset of synesthesia, and whether the different types of synesthesia have different types of causes and triggers remain relatively unknown. Here we review a variety of studies of human subjects, looking at the effects of drug-induced synesthesia with the aim of identifying its possible causes and underlying mechanism. Two distinct hypotheses for the nature of the mechanism underlying drug-induced synesthesia are proposed.

2. Drug-induced synesthetic experiences and other hallucinogenic effects

The effects of hallucinogens can be characterized as visual disturbances and range from experientially simple contours to surrealistic images, such as oddly shaped objects with multicolored contours, images with ornamental or kaleidoscopic compositions, and altered scenes. The drawings in **Fig. 4**, made by an artist under the influence of LSD, illustrate the perceptual changes experienced during different stages of intoxication (Bercel et al., 1956).

Subjects exposed to hallucinogens frequently report enhanced color perception and vividly colored visual disturbances (Hartman & Hollister, 1963; Studerus et al., 2011). It may be thought that these experiences are not really synesthetic, as they may appear merely to be the result of increased sensitivity to the spectral properties that normally give rise to color experience. However, evidence of increased thresholds for axonal responses beyond the thalamic synapses during exposure coupled with increased absolute and differential limens of vision challenge this hypothesis (Evarts et al., 1955; Carlson, 1958; Bishop et al., 1958; Hollister and Hartman, 1962; Hartman & Hollister, 1963).[4]

[4] Colored visions experienced under the influence of hallucinogens seem paradoxical in view of increased thresholds for axonal responses beyond the thalamic synapses (since the thalamus is the bridge connecting sensory paths) unless we assume that synesthesia is occurring (Hartman and Hollister, 1963). The term ‘absolute limen of vision’ refers to a sensory threshold and is the minimum amount of stimulation required for an organism’s sense organs (such as color vision) to detect a stimulus (such as a color) fifty percent of the time. The term ‘differential limen of vision’ refers to the smallest change in a stimulus such as a color that can be detected by an organism. Carlson (1958) reported that LSD decreases both the photopic (which functions primarily due to cones in the retina, which are responsible for color perception) and scotopic (which functions primarily due to rods in the retina, which are responsible for monochromatic vision in very low light) thresholds to light in humans. Since color vision requires photopic vision, the fact that LSD decreases the photopic threshold indicates a depression in the activity of cone based retinal and/or central mechanisms that mediate color perception. This, in turn, decreases the ability of subjects to accurately discriminate between stimuli of adjacent hues (as shown by Hollister and Hartman, 1962).

Moreover, Hartman and Hollister (1963) tested the hypothesis that hallucinogens interfere with the normal integration of experience within specific sensory modalities. Specifically, they studied the effects of stimuli varying in degree of adequacy for evoking color experience (such as discrimination of hues, reports of colors of after-images, and color perception induced by achromatic stimuli) before and during the administration of mescaline, LSD, and psilocybin. The team found that all three hallucinogenic drugs triggered cases of color experience elicited by a variety of stimuli, regardless of whether these stimuli (a) normally elicit or imply color experience (such as stimuli that generate after-images), (b) marginally elicit color experiences (flicker stimuli), or (c) never elicit color experience or other visual effects (pure tones). Each of these drugs was found to have different illusory hallucinogenic effects. While all three drugs gave rise to an increased reporting of after-images, psilocybin decreased hue discrimination significantly by comparison to the other two drugs (which also decreased hue discrimination). Mescaline and LSD gave rise to more color experiences from flicker stimuli than psilocybin. The color experiences elicited by LSD significantly increased when flicker stimuli were combined with pure tones. LSD and mescaline significantly increased colors and patterns elicited by pure tones while the spectral patterns that were evoked varied slightly among the three drugs. Although stimuli that evoke color experiences (in category *a* above) were enhanced by hallucinogens, hue discrimination was actually slightly decreased (Hartman and Hollister, 1963). These findings indicate that enhanced color perception and vividly colored visual disturbances typically associated with hallucinogens are not simply a case of increased sensitivity to spectral properties. Visual disturbances produced by hallucinogens are thus better understood as a kind of drug-induced synesthesia (Shanon, 2002, 2003; Studerus et al., 2011; Sinke et al., 2012, Brogaard, 2013).

Most hallucinogens (including LSD, psilocybin, and mescaline) have been found to transiently induce synesthetic experiences (Luke & Terhune, 2013). Subjects treated with such drugs frequently report experiencing an altered perception of the world that blends sensory modalities that normally are informationally encapsulated. Colored music is the most frequently reported type of drug-induced synesthesia (Shanon, 2002, 2003; Studerus et al., 2011; Sinke et al., 2012).

LSD and mescaline tend to induce a greater variety of synesthesia than psilocybin. LSD is regularly reported to give rise to auditory-visual, music-visual, color-gustatory, color-auditory and music-olfactory synesthesias (Hartman & Hollister, 1963, Hollister & Hartman, 1962; Masters & Houston, 1966) whereas mescaline frequently triggers haptic-visual, auditory-visual, kinaesthetic-visual

and algesic-color synesthesias (Kelly, 1934; Hartman & Hollister, 1963).[5] By contrast, subjects exposed to psilocybin tend to report having some form of auditory-visual synesthesia (Hollister & Harman, 1962; Carhart-Harris et al., 2011). Interestingly, subjects with developmental auditory-visual synesthesia who were treated with mescaline reported various novel forms of synesthesia, including auditory-visual, tactile-visual, olfactory-visual, visual-tactile, olfactory-tactile, kinesthetic-visual, algesic-visual, and visual-thermal synesthesias (Simpson & McKellar, 1955). Collectively, these studies strongly suggest that hallucinogens can, and often do, induce synesthetic experiences in non-synesthetic subjects as well as novel synesthetic experiences in subjects with developmental synesthesia.

In addition to synesthetic experiences, hallucinogens tend to also induce hallucinatory and illusionary experiences. It is not entirely clear what distinguishes drug-induced synesthetic experiences from drug-induced hallucinations or illusions. Reported visual disturbances include experiences of external objects having an unusual variety of colors, textures and shapes and undergoing swift changes. Subjects sometimes describe seeing melting windows, breathing walls, or spiraling geometrical figures hovering over the surfaces of objects (Brogaard, 2013). Cott and Rock (2008) encountered a subject who described having the following experience: “The room erupted in incredible neon colors, and dissolving into the most elaborate incredibly detailed fractal patterns that I have ever seen.” Many authors characterize such experiences as hallucinatory rather than synesthetic (Cott & Rock, 2008; Hartman & Hollister, 1963; although see Studerus et al., 2011).

While it is admittedly difficult to distinguish between illusionary or hallucinatory experiences and synesthetic experiences, there are at least three crucial differences between the good and the bad cases (Sagiv et al., 2011; Brogaard, 2013). Firstly, unlike synesthetic experiences, hallucinations proper do not have a phenomenally apparent inducer (Slade & Bentall, 1988). Secondly, typical hallucinations tend not to be predictable; we cannot predict the type of hallucination one may have by simply knowing the stimuli that gave rise to it (Van Campen, 2007; Cytowic & Eagleman, 2009). The typical associations between inducer-concurrent pairs, by contrast, make synesthetic experiences far more predictable. Thirdly, whereas illusions and hallucinations often trigger a feeling as of the experience being veridical, synesthesia very often does not trigger this feeling (Terhune & Cohen Kadosh, 2012; Hermle et al., 2012). It should be noted, of course, that while these particular marks distinguish developmental and acquired synesthesia from hallucinations, they do not always pertain to drug-

[5] Algesic-color synesthetes associate pains with colors.

induced synesthesia, as the latter is not always predictable and often triggers a feeling of veridicality.

Some visual disturbances such as intensified colors for brief periods of time, flashes of color, and illusions of movement in the peripheral visual field persist for weeks, months, and even years after exposure to hallucinogens (Horowitz, 1969; Abraham, 1983). These recurrent experiences following drug exposure are also known as flashbacks. Abraham (1983) found no linear relationship between the total number of reported LSD exposures and the number of flashbacks experienced. However, a significant correlation between dose and the number of flashbacks subjects experienced was observed, reaching a plateau after it peaked, first at 15 and then at 40 exposures.

On rare occasions, subjects develop hallucinogen-persisting perceptual disorder (HPPD) after LSD abuse. A 33-year-old female subject, who developed HPPD after abusing LSD for one year at the age of 18, reported that she was experiencing after-images, perception of movement in the periphery of her visual field, blurring of small patterns, halo effects, as well as macropsia (objects appearing larger than normal) and micropsia (objects appearing smaller than normal) (Hermle et al., 2012).[6] It is likely that there is a genetic basis to LSD sensitivity leading to HPPD, although the condition tends to occur only after prolonged exposure to the drug (Abraham, 1983).

Hallucinogen-induced flashbacks differ from synesthetic experiences insofar as they occur in the absence of an inducer. They are typically treated as pseudohallucinations because subjects recognize their unreal nature (Abraham, 1983; Hermle et al., 2012). Their occurrence may nevertheless be able to provide us with a better understanding of drug-induced synesthesia, as they allow us to study the neural regions they activate and compare them to those implicated in drug-induced synesthesia.

3. The causal role of serotonin receptors in hallucinogenic effects

Despite prodigious research on synesthesia, the mechanistic commonalities (if any) among the different types, the cause of their onset, and whether different types have different causes remain unknown. Direct or indirect projection through

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[6] Hermle et al. (2012) observed that although previous treatments with antidepressants failed to ameliorate her symptoms, the antiepileptic lamotrigine completely eliminated the visual disturbances she experienced. Not only does this study provide a new approach to the treatment of HPPD, as the authors suggest, but it can also provide some insight into the mechanisms of drug-induced synesthesia: if antiepileptic drugs are successful in eliminating HPPD resulting from the abuse of hallucinogens, it stands to reason that there might be neurophysiological similarities between the mechanisms of epilepsy and drug-induced synesthesia. The hippocampus, which is a particularly important cortical structure in the pathophysiology of one of the more common epilepsy syndromes (Babb & Brown, 1987), is also critical in synesthetic experience (Cytowic, 1997).

increased structural connectivity mechanisms (Ramachandran & Hubbard, 2001a, 2001b; Hubbard et al., 2005; Rouw & Scholte, 2007; Jancke et al., 2009; Hanggi et al., 2011; Zamm et al., 2013), functionally-driven disinhibited-feedback mechanisms (Grossenbacher & Lovelace, 2001; Dixon et al., 2006; Esterman et al., 2006; Neufeld et al., 2012), and mixed models (Hubbard, 2007; Ward, 2013) have been proposed to explain the mechanisms underlying the occurrence of synesthesia.[7]

Moreover, although all three types of synesthesia are often discussed in the literature as being on a par, there are more differences than similarities between drug-induced synesthesia and its developmental or acquired counterparts (Sinke et al., 2012). Given that experiences causally supervene on neurological processes, significant differences in the phenomenology of experience should correlate with significant differences in neurological underpinnings (Brogaard, 2013). The phenomenological differences among developmental and acquired synesthesias, on the one hand, and drug-induced synesthesia, on the other, suggest that the neural mechanisms underlying the drug-induced forms must be quite different from the mechanisms underlying the developmental and acquired forms.

It has been proposed that structural connectivity involving unusual anatomical connectivity between color or sound areas and the fusiform gyrus are present in early childhood in the majority of individuals (Kennedy et al., 1997; Hubbard, 2007). These excessive projections then undergo extensive pruning during childhood and adolescence (owing to the loss of serotonin-terminals) (Ramachandran & Hubbard, 2001a & 2001b; Hubbard et al., 2005). In synesthetes, this type of pruning may be incomplete, leaving unusual structural connectivity among, say, the shape and color brain regions. There is recent evidence in support of this hypothesis for grapheme-color synesthesia (Rouw & Scholte, 2007; Jancke et al., 2009; Hanggi et al., 2011) as well as sound-color synesthesia (Zamm et al., 2013). In both cases, the synesthesia appears to be the result of direct projections from form to color or sound areas.

Since drug-induced synesthesia is transiently induced, it is likely that its occurrence cannot be attributed to altered structural connectivity in the brain. While developmental and acquired synesthesias involve morphological substrates (Sinke et al., 2012), drug-induced synesthesia is likely linked to functional changes in brain activity (Hubbard and Ramachandran, 2005; Sinke et al., 2012; Carhart-Harris et al., 2012; Brogaard, 2013), although it may also reinforce existing morphological structures (Brogaard, 2013). The fact that

[7] Whether a structural connectivity mechanism underlies drug-induced synesthesia could be tested by using a DTI paradigm to determine whether there are similar patterns of localized hyper-cortical-connectivity in individuals who experience drug-induced synesthesia (Brogaard, 2013).

hallucinogens can produce novel types of synesthesia in developmental synesthetes seems to provide evidential support for these hypotheses (Simpson & McKellar, 1955). Additional empirical studies indicate functional as opposed to structural changes in connectivity in subjects exposed to hallucinogens. Comparing the resting-state functional brain activity in 15 healthy subjects after intravenous infusion of psilocybin and placebo, Petri et al., (2014) found that the homological structure of the brain's functional patterns undergoes a dramatic change after the administration of psilocybin, which is not observed in the placebo case. These changes owing to the administration of psilocybin are characterized by the occurrence of numerous transient structures of low stability and a few persistent ones (compare circles *a* and *b* in **fig. 5**).

It is commonly assumed that the functional changes in brain activity elicited by hallucinogens are due to increased neural activity. For example, hallucinogenic effects have been found to correlate with increased metabolic activity in the frontomedial and frontolateral cortices, anterior cingulate, and temporomedial cortex (Vollenweider et al., 1997). However, a study using fMRI mapping of the cerebral blood flow in 15 healthy, hallucinogen-experienced subjects before and after intravenous infusion of psilocybin and placebo revealed that psilocybin significantly decreased the positive coupling of medial prefrontal cortex and posterior cingulate cortex (two key structural hubs) (Carhart-Harris et al., 2012; see also Lee & Roth, 2012). The function of the posterior cingulate cortex is not fully understood. However, its association with the default-mode network regions (Raichle et al, 2001), which are known to host the highest number of cortico-cortical connections in the brain, suggests that it may play a functional role in consciousness and high-level constructs such as the self (Raichle, 1998; Gusnard et al, 2001). This might account for the fact that functional decreases in activity in posterior cingulate cortex alter the conscious states of subjects under the influence of psilocybin (Carhart-Harris et al., 2012). Of course, given the diversity of both the chemistry and the effects of hallucinogens, the functional changes in brain activity produced by psilocybin may not be applicable across the board. For example, it may turn out that the functional changes produced by psilocybin differ from those produced by LSD, mescaline, or other hallucinogens. Future studies may reveal functional differences in brain activity among these drugs. For example, it may turn out that the hallucinogenic effects of semi-synthetic drugs, such as LSD, work by increasing neural activity in cortico-cortical networks.

Functional changes in brain activity caused by hallucinogens in the serotonin agonist class are initiated at the receptor level by serotonin receptor activity (Nichols & Nichols, 2008). Studies show that the effects of these hallucinogens, including synesthesia, are the result of stimulation of the 5-HT2A

(and possibly the 2C) subtype(s) of the 15 different serotonin receptors (5-hydroxytryptamine or 5-HT). Other receptor types may nevertheless play a role in producing altered states of consciousness, especially in the case of the less "clean" hallucinogens such as LSD (Glennon et al., 1984; Nichols, 1986; Glennon, 1990, 1996; Blair et al., 2000; Nichols, 2004). Although serotonin agonists like LSD bind to different serotonin receptor subtypes as well as other monoamine receptors, including the dopamine receptors D1 and D3, their synesthetic effects appear to be the result of their affinity for the 5-HT2A serotonin receptor (Vollenweider & Kometer, 2010; Ray, 2010; Brogaard, 2013).

Hallucinogens that function primarily as serotonin agonists tend to induce transient auditory-visual synesthesia by binding to 5-HT2A serotonin receptors, thereby producing an excitatory response of sensory cortical networks (Brogaard, 2013).[8] Two major classes of hallucinogens, indoleamines (LSD and psilocybin) and phenethylamines (mescaline), are potent partial agonists at 5-HT1A/2A/2C receptors. But only 5-HT2A receptor activation appears to be directly correlated with altered perceptual states, including synesthesia (Glennon, 1990; Vollenweider et al., 1998; Nichols, 2004; Presti & Nichols, 2004; although see Previc 2011 for a different perspective).

Serotonin can serve both as an inhibitory and an excitatory neurotransmitter in different regions of the brain (Lee & Roth, 2012), which may explain the seemingly conflicting findings that hallucinogens work by increasing neural activity as well as by decreasing it (although, as we suggested above, it may turn out that some hallucinogens increase neural activity while others decrease it). For example, serotonin has been found to have an excitatory effect when binding to 5-HT2A serotonin receptors on the dendrites of layer V pyramidal neurons but to exert an inhibitory effect on cortical brain activity when reducing fear processing in the amygdala via GABA modulation (Barkai & Hasselmo, 1994; Aghajanian & Marek, 1999).[9]

Drugs that inhibit serotonin receptor activity, by contrast, have been found to produce the opposite effects. Prozac (fluoxetine), a selective serotonin reuptake inhibitor that increases 5-HT1 receptor activity (Marek et al., 2003), was found to block synesthesia in two subjects, whereas the anxiolytic drug Wellbutrin (bupropion), which inhibits 5-HT2A receptor activity, was found to temporarily abolish synesthesia in one subject (Brang & Ramachandran, 2007).

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[8] Synesthesia acquired after brain injury, by comparison, has been linked to local neurotransmitter flooding—caused by an excessive release of serotonin and glutamate following necrosis due to tissue damage—leading to increased functional or structural interconnectedness among different brain regions (Busto et al., 1997; Hinzman et al., 2010).

[9] Studies using electroencephalogram (EEG) show that activation of 5-HT2A serotonin receptors increases the excitability of cortical sensory networks by modulating alpha oscillations (Kometer et al., 2013).

The synesthetic effects of psilocybin can be blocked (dose-dependently) by ketanserin (a 5-HT2A antagonist) and the atypical antipsychotic risperidone but can be triggered or intensified by haloperidol (a dopamine antagonist and typical antipsychotic) (Vollenweider et al., 1998). This adds further evidence to the hypothesis that the 5-HT2A receptor plays a crucial role in drug-induced synesthesia.[10]

Studies have consistently suggested that 5-HT2A serotoinin receptor activation of cortical neurons is responsible for mediating the signaling pattern and behavioral responses (Presti & Nichols, 2004; González-Maeso et al., 2008; Nichols & Nichols, 2008). However, 5-HT2A receptor activation of cortical neurons is not sufficient to produce hallucinogenic effects. Both LSD and lisuride (a non-hallucinogenic drug) were found to regulate signaling in the same 5HT2A-expressing cortical neurons, but only LSD activated additional signaling pathways ($G_{i/o}$ and $G_{q/11}$ protein pathways) suggesting that the coactivation of other pathways is required to produce hallucinogenic effects (González-Maeso et al., 2007; see also Schmid & Bohn, 2010).

Stimulation of 5HT2A receptors by 5HT2A agonists causes activation of pyramidal neurons in cerebral cortex by enhancing glutamatergic neurotransmission within intracortical networks, especially those involving cortical layer V (Aghajanian & Marek, 1999a; Puig et al., 2003; Beique et al., 2007; Zhang & Marek, 2008). Recent studies suggest that co-transmission of serotonin and glutamate frequently occurs in the central nervous system (Trudeau, 2004; Ciranna, 2006). In addition, 5-HT2A serotonin receptors have been found to increase glutamate release (Ceglia et al., 2004; Torres-Escalante et al., 2004). There is additional evidence suggesting that psilocybin targets the cortical receptor complex that forms when the metabotropic glutamate mGlu2 receptor interacts with 5-HT2A serotonin receptors (González-Maeso et al., 2008; Woolley et al., 2008; Moreno et al., 2011; see also Field et al., 2011).[11] Increased release of glutamate in response to hallucinogen administration is likely to enhance cortical metabolic activity (Vollenweider et al., 1997). The resulting increased excitatory action of serotonin and glutamate in sensory regions might explain why hallucinogens mimic the perceptual aspects of psychosis, especially schizophrenia (Aghajanian & Marek, 1999; Pralong et al., 2002; Nichols, 2004; González-Maeso et al., 2008).

Some hallucinogens, notably psilocybin, may be able to alleviate the symptoms of a variety of mental illness, including obsessive-compulsive disorder,

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[10] See also Hall et al. (1995) who tested for both clozapine and risperidone.

[11] In *postmortem* human brains from untreated schizophrenic subjects, the 5-HT2A was found to be up-regulated while the mGluR2 was found to be down-regulated (see González-Maeso et al., 2008). This is relevant because hallucinogens mimic the perceptual aspects of schizophrenia (Aghajanian & Marek, 1999; Pralong et al., 2002; Nichols, 2004; González-Maeso et al., 2008)

anxiety, depression, as well as alcoholism and nicotine dependence (Grob et al., 2011; Moreno et al., 2006; Bogenschutz, 2013). Moderate doses of psilocybin have been found to improve mood and anxiety in patients with advanced-stage cancer suffering from anxiety or depression (Grob et al., 2011). The exact mechanisms behind the therapeutic effects of hallucinogens are not well understood. However, recent findings suggest a possible explanation of the alleviation of depression by psilocybin. We know, for example, that activity in the medial prefrontal cortex is known to elevate in depression (Holtzheimer and Mayberg, 2011) and that it is deactivated by psilocybin (Carhart-Harris, 2012). We also know that depression is linked to deficient 5-HT2A receptor stimulation, particularly in the medial prefrontal cortex (see Bhagwagar et al, 2006). Lastly, we know that psilocybin activates 5-HT2A receptors that are usually deficient in subjects suffering from depression (Bhagwagar et al, 2006), thereby deactivating medial prefrontal cortex as well as important connector hubs, such as the thalamus[12] and posterior cingulate cortex (Carhart-Harris et al., 2012; Lee & Roth, 2012). Findings suggest that it is the ability of psilocybin to deactivate the medial prefrontal cortex (a region that exhibits disproportionately high activity under normal conditions, see Raichle et al, 2001) that leads to (temporary) alleviation of depression. Perhaps a similar mechanism underlies other hallucinogens such as LSD and mescaline.

Hallucinogens are considered physiologically safe and do not produce dependence (Nichols, 2004; Studerus et al., 2011). Several safeguards must, nevertheless, be adhered during treatment to minimize or avoid adverse risks, known colloquially as “bad trips”, that could lead to potentially dangerous behavior (Hasler et al., 2004; Johnson et al., 2008). The recommended safeguards researchers must adhere to in order to minimize or avoid potential adverse risks include excluding volunteers with personal or family history of psychotic or other severe psychiatric disorders, establishing trust with volunteers, carefully preparing them for treatment, and providing a safe environment as well as interpersonal support from at least two study monitors during each session. The administration of psilocybin, although not hazardous to somatic health for healthy subjects, can temporarily increase blood pressure (Hasler et al., 2004). Therefore, its administration may be hazardous for subjects suffering from cardiovascular conditions, especially untreated hypertension.

[12] Lesions to thalamocortical terminals alter 5-HT2A receptor binding in the prefrontal cortex (see Marek et al., 2001). In addition, thalamic lesions selectively decreased the frequency of serotonin-induced excitatory postsynaptic currents recorded from layer V pyramidal cells by 60 percent. Large bilateral lesions of the amygdala, by contrast, did not alter the frequency of serotonin-induced excitatory postsynaptic currents recorded from layer V pyramidal cells (Marek et al., 2001).

4. The mechanisms of drug-induced synesthesia

There is little doubt that both serotonin and glutamate receptor systems play a crucial role in the mechanisms of action of hallucinogens in the serotonin-agonist family. However, what continues to remain elusive is the specific mechanism that underlies the occurrence of drug-induced synesthesia. One suggestion for its occurrence is that altered feature binding within a given network of active regions leads to altered perceptual experiences. Using dynamic causal modeling for fMRI, Van Leeuwen et al. (2011) showed that the differences in the perceptual experiences between projectors and associators (developmental) synesthetes result from differences in the connectivity within the grapheme–color synesthesia network. The team found that V4 cross-activation in grapheme–color developmental synesthetes was induced via a bottom-up pathway (within the fusiform gyrus) in projectors but via a top-down pathway (via the parietal lobe) in associators.

Since developmental synesthesia involves structural rather than functional brain connectivity, it is unlikely that these findings can provide an insight into the mechanisms underlying the perceptual experiences of drug-induced synesthesia. It is more likely that the qualitative diversity of the experiences produced by hallucinogens in the serotonin-agonist family is due to their diverse patterns of interaction with different classes of receptors. A recent study of the receptor binding profiles of thirty-five hallucinogenic drugs (twenty-five of which appear in **fig. 6**) assayed against fifty-one receptors, transporters, and ion-channels shows that hallucinogens have very diverse patterns of interaction with different classes of receptors (Ray, 2010). For example, while mescaline was found to be the only drug to have the greatest affinity for the adrenergic receptor, LSD was found to have the strongest interaction collectively with the five dopamine receptors (D1, D2, D3, D4, D5), ten assayed 5-HT receptors, and four assayed 5-HT1 receptors (Ray, 2010). However, although it is possible that this diversity of receptor interaction may be implicated in the qualitative diversity of the experiences produced by different hallucinogens, it is, by itself, insufficient to explain the mechanisms underlying drug-induced synesthesia.

Brogaard (2013) has suggested a model for how auditory-color synesthesia might arise in cases of psilocybin-induced synesthesia. The core of the hypothesis supporting the model is that qua serotonin-agonist psilocybin binds to the 5-HT2A receptors in layer V pyramidal cells. We know from previous studies that this increases glutamate levels locally (Aghajanian & Marek, 1999a; Puig et al., 2003; Beique et al., 2007; Zhang & Marek, 2008). Layer V pyramidal cells unify multisensory information through feedback loops that synchronize oscillatory neural responses (Guillery & Harting, 2003). In the visual and the auditory cortices, layer V neurons form feedback loops with local neurons as well

as neurons in the thalamus and prefrontal cortex. Thalamic projections play a role in discriminating among incoming information and integrating information from different sensory channels while prefrontal cortical projections play a role in higher-order cognitive processes and the generation of conscious representation.

In normal multisensory perception, when the spatial and temporal attributes of incoming signals match, low-level multisensory binding of incoming signals from auditory and visual channels occurs spontaneously in the auditory cortex via thalamocortical feedback loops (Schroeder & Foxe, 2005). However, excessive excitatory activity in layer V pyramidal neurons results in a destabilization of layer V projections to the thalamus via GABAergic neuronal circuits (Kim & McCormick, 1998; Markram et al., 2004), giving rise to various effects, including decreased attentional discrimination among incoming stimuli (allowing more information to flood the sensory cortices), loss of stimulus-specific inhibition, and increase of random (or environmentally under-constrained) thalamic activity.

The most relevant effect of the destabilization of layer V projections to the thalamus via GABAergic neuronal circuits in the search for the mechanisms underlying drug-induced synesthesia is disruption of low-level, spontaneous integration of multisensory stimuli on the basis of actually matching spatial and temporal attributes (Behrendt & Young, 2004; Sagiv et al., 2011). This disruption can result in incongruent experiences, such as hearing an object hit the floor prior to seeing it fall and possibly a coupling of stimuli that do not belong together.[13] The fact that colored, geometrical grids, matrices or fractals induced by music is a common drug-induced synesthetic experience suggests a plausible mechanism for drug-induced synesthesia (Brogaard, 2013). The hypothesis then is that the brain assumes that experiences resulting from occipital processing of random thalamic activity match auditory stimuli, which leads to an unusual low-level binding in the auditory cortex (see **Fig. 7).** It is plausible that this aberrant binding leads to an experience of the two distinct inputs (color and music) as an inducer-concurrent pair, for example, colored, geometrical music (Brogaard, 2013).

4. Inhibition and Embodied Cognition

Another insight into the mechanisms of drug-induced synesthesia comes from what is sometimes called the embodied cognition hypothesis (Gray & Simner, 2015). Accordingly, how we conceive of the world is grounded in and constrained by the nature of our perception-action systems (Shapiro, 2011; for a review see Wilson & Golonka, 2013). For example, seeing someone being touched is

[13] It should be noted that certain visual disturbances (mainly hallucinations) frequently occur without an inducer, most likely as a result of random activity in the thalamus (Behrendt & Young, 2004; Sagiv et al., 2011).

thought to induce activity in the tactile sensory areas. In non-synesthetes, this induced activity may not reach conscious awareness (Brogaard, In Press). This is different in a case like mirror-touch synesthesia, where observing another person being touched induces a tactile sensation on the synesthete's own body. For some subjects with mirror-touch synesthesia the tactile sensation is experienced in the same anatomical areas as the observed touch, while for others it is experienced in anatomical areas that are opposite of those activated by observed touch (for example, an observed touch of another person's right cheek is experienced on the synesthete's left cheek) (Banissy et al., 2008).

Another example of embodied cognition involves cases in which words reinstate neural activity in the brain regions that process sensory input from the word's referent (for a review, see Willems & Casasanto, 2011). Action-related sentences, which describe actions with different effectors such as *I grasp the knife*, *I bite an apple,* and I *kick the ball*, activate the premotor cortex in an effector-specific manner (Willems et al., 2010; Aziz-Zadeh et al., 2006; Tettamanti et al., 2005; Brogaard, In Press). Action-related nouns and verbs such as *bookend*, *clock*, *door*, *cup* and *hammer*, also activate premotor and inferior parietal areas, and the amount of action associated with an object word is reflected in the activation of the motor system during word reading (Rueschemeyer et al., 2010). Bookends, clocks, cups, and hammers differ with respect to how much action is needed to use the object effectively. Objects like hammers and cups that need active manipulation give rise to higher levels of neural activation than objects like bookends and clocks that can be used without actively manipulating them. Similar observations have been made for action verbs such as *kick*, *jump*, and *run* (Kim, 2014) as well as verbs such as *glowing*, *hopping*, and *squeaking* (Bedny and Caramazza, 2011).

Something similar is occurring in the case of lexical-gustatory synesthesia (Ward et al., 2005; Gray & Simner, 2015). For example, it has been found that 'peach' reinstates neural activity in brain regions that compute the taste of peaches (Ward et al., 2005). While in non-synesthetes the taste sensation is inhibited, meaning it is not accessible to consciousness, in individuals with lexical-gustatory synesthesia the sensation is disinhibited. As a result, subjects with lexical-gustatory synesthesia consciously perceive the taste of peaches when hearing the word 'peach'. Studies further suggest that synesthetic tastes spread throughout the lexicon along the same connections facilitating phonological priming effects, and further, that hearing a word and experiencing a taste frequently strengthens these connections (Simner & Haywood, 2009; Ward et al., 2005). For example, hearing 'reach' may activate an associative connection to the word 'peach,' thereby inducing the taste of peaches while hearing 'reach.' Frequent experiences of the taste of peaches can then

strengthen the connection between ‘reach’ and the taste of peaches. Following this spreading, individuals with lexical-gustatory synesthesia would experience tastes not only for words with which they are originally associated (such as the taste of peach and ‘peach’), but also for other (seemingly unrelated) words in their mental lexicon (such as ‘reach’).

Gray and Simner (2015) hypothesize that links between associations (such as the taste of peach) and words (such as ‘peach') may be consciously experienced by synesthetes due to disinhibited or over-exuberant activation that is normally subdued in non-synesthetes. One piece of evidence they provide in favor of this hypothesis is that hallucinogens can unlock the disinhibition. The serotonin-model for how hallucinogens give rise to synesthesia may provide further evidence in favor of Gray and Simner’s hypothesis. Anecdotally, at least, psilocybin sometimes triggers lexical-gustatory synesthesia. While the serotonin model was originally proposed as an explanation for drug-induced auditory-visual synesthesia, it is plausible that it extends to other forms of the condition, such as lexical-gustatory synesthesia.

One possibility is that excessive excitatory activity in brain regions processing gustatory stimuli results in a destabilization of projections to the thalamus through GABAergic neuronal circuits. This increases random thalamic activity, which is then processed in brain regions processing gustatory stimuli. The brain then assumes that an experience that results from gustatory processing of random thalamic activity matches linguistic stimuli, which then leads to unusual binding processes associating words and taste sensations. However, as this mechanism does not implicate an activation of similar multisensory binding in non-synesthetes, it does not support the Gray-Simner claim that lexical-gustatory synesthesia originates in a release of normally inhibited multisensory binding.

Another possibility is that the destabilization of projections to the thalamus through GABAergic neuronal circuits leads to decreased attentional discrimination among incoming stimuli, allowing more information to become accessible to consciousness. Taste experiences that are normally unconsciously triggered by lexical items, as suggested by Gray and Simner, may be among those neural activities that are inhibited in non-synesthetes but are released into working memory when the projections to thalamus become disinhibited.

Although the above hypotheses are aimed at explaining auditory-color and lexical-gustatory drug-induced synesthesias, they may be applicable to other types of drug-induced synesthesia. According to the first proposed explanation of lexical-gustatory synesthesia, a destabilization of projections to the thalamus through GABAergic neuronal circuits leads to decreased attentional discrimination among incoming stimuli, allowing more random information to

become accessible to consciousness. This mechanism may be generalizable to other types of drug-induced synesthesia. According to the second proposal, taste experiences that are regularly unconsciously triggered by lexical items may be among those neural activities that are inhibited in non-synesthetes but are released into working memory when the projections to thalamus become disinhibited. It is plausible then that the experience of unusual binding of other types of stimuli, for example, a binding of music and color may be explained in a similar fashion. Color experiences that are commonly unconsciously triggered by musical notes could be among those neural activities that are inhibited in non-synesthetes but are released into working memory when thalamic projections become destabilized.

This suggests a slight variation on the model of drug-induced synesthesia presented in the previous section. While random information from the thalamus likely binds with sensory input in some cases of drug-induced synesthesia, it is also possible that the destabilization of thalamic projections decreases attentional inhibition, which would then allow increased attention and awareness of normal stimuli-binding.

5. Conclusion

Studies indicate that both serotonin and glutamate receptor systems may play a crucial role in the mechanisms of action of hallucinogens in the serotonin agonist family. What continues to remain elusive, however, is the specific mechanism that underlie the occurrence of drug-induced synesthesia. We proposed two distinct hypotheses about how various types of drug-induced synesthesia may arise.

The first hypothesis is that the drug-induced destabilization of layer V thalamic projections via GABAergic neuronal circuits from sensory areas leads to a disruption of low-level, spontaneous integration of multisensory stimuli. In subjects who are not exposed to hallucinogens, this sort of spontaneous integration regularly occurs on the basis of actually matching spatial and temporal attributes. Destabilization of feedback loops, however, may result in binding incongruent features or binding of random thalamic activation with sensory input in the sensory cortices.

The second hypothesis builds on observed forms of embodied cognition, cases in which perceptual experiences of external stimuli may activate task-related neural areas. In subjects who are not exposed to hallucinogens, the binding of perceptual and task-related features is not accessible to consciousness. However, hallucinogens may lead to decreased attentional discrimination among incoming stimuli, resulting in awareness of the atypical

binding that is already present in non-synesthetes who are not exposed to synesthesia-inducing drugs.

Both hypotheses seem consistent with empirical studies implicating the effects of hallucinogens with functional changes of brain regions such as the thalamus and the prefrontal cortex arising from 5-HT2A receptor activation, particularly those expressed in neocortical pyramidal cells (Nichols, 2004; Vollenweider et al., 1997; Kometer et al., 2013; Carhart-Harris et al., 2012; Lee & Roth, 2012). We may nevertheless be able to empirically establish which of the two hypotheses has a higher degree of credibility by looking closer at the speed of the responses of subjects (who, under the influence of hallucinogens, associate different stimuli such as sounds and colors) in placebo priming experiments.

Given the first hypothesis, we should expect that increased thalamic activation in subjects under the influence of hallucinogens would activate different sensory modalities that would not typically be activated in placebo cases. For example, suppose that thalamic disturbances activated both the sound and color areas in subjects under the influence of hallucinogenic drugs but not in placebo cases. This would suggest that atypical binding of sensory input in particular sensory modalities is taking place. Such findings would provide some evidential support for the first hypothesis.

Given the second hypothesis, we should expect subjects not exposed to drugs to be able to respond in particular ways in priming experiments (given that they are making the association already but unconsciously). Suppose, for example, that subjects under the influence of hallucinogens associate a particular sound with the color orange. We should expect these subjects to respond more quickly or accurately to orange stimuli compared to, say, blue stimuli, when primed with that particular sound when they are not under the influence of hallucinogens. Such findings would provide some evidential support for the second hypothesis. Of course, it is also plausible that both mechanisms may underlie different instances of drug-induced synesthesia.

[10] Applications to Other Addictions and Substance Misuse

Peyote (from which mescaline is derived), phencyclidine (PCP), dimethyltryptamine (DMT), datura, Ergoline alkaloids, Harmala alkaloids Nuciferine, aporphine, cathinone, THC, nicotine.

[11] Mini-Dictionary of Terms

Hallucinogens (also known as psychedelics, psychotomimetics, or entheogens). Psychoactive substances known to (dose-dependently) induce profound changes in perception, including changes in the experience of time or space, as well as alterations in moods, thoughts, and other mental states (psilycybin, LSD, mescaline).

Synesthesia: involves either the stimulation of one sensory modality giving rise to an experience in a distinct sensory modality (such as when a smell or taste gives rise to a color experience) or the stimulation of a single sensory modality giving rise to an unusual qualitative experience (such as when an achromatic grapheme appears colored).

Drug-induced Synesthesia: the type of synesthesia that tends to be experienced (almost exclusively) during exposure to hallucinogenic substances.

Inducer: The trigger of a synesthetic experience (a grapheme or a sound).

Concurrent: the experience to which the inducer gives rise (the synesthetic color associated with a grapheme or a sound).

HPPD: hallucinogen-persisting perceptual disorder associated with the abuse of hallucinogenic substances.

Pseudohallucinations: hallucinations whose unreal nature is recognized by subject having them.

Structural Connectivity: anatomical connectivity in the brain.

5-HT2A: 5-hydroxytryptamine 2A subtype of the 15 different serotonin receptors.

S**erotonin receptor agonists:** compounds that activates serotonin receptors in a manner similar to serotonin.

Thalamus: a structure in the middle of the brain, located between the cerebral cortex and the midbrain, which correlates several important processes, including consciousness, sleep, and sensory interpretation.

***Gamma*-Aminobutyric Acid** (**GABA):** the key inhibitory neurotransmitter in the mammalian central nervous system playing the principal role in reducing neuronal excitability throughout the nervous system.

[12] Key Facts of Functional Connectivity

- Unlike developmental and acquired synesthesias, drug-induced synesthesia is likely linked to functional changes in brain activity (see Legend to Fig. 5 below).
- Functional changes in brain activity caused by hallucinogens in the serotonin agonist class are initiated at the receptor level by serotonin receptor activity.

Legend to Fig. 5: This is an illustration of the connections between neurological activity in subjects given a placebo (a) and those given psilocybin (b). From Petri et al. (2014).

Key Facts of 5-HT2A receptors

- Serotonin can serve both as an inhibitory and an excitatory neurotransmitter in different regions of the brain.
- 5-HT2A receptor activation of cortical neurons is not sufficient to produce hallucinogenic effects.
- This suggests that the coactivation of other pathways is required to produce hallucinogenic effects.

Key Facts of the therapeutic effects of Hallucinogens

- Some hallucinogens, notably psilocybin, may be able to alleviate the symptoms of a variety of mental illness, including obsessive-compulsive disorder, anxiety, depression, as well as alcoholism and nicotine dependence.
- Early cultures, including various groups of indigenous peoples native to the central or southern regions of Mexico, used hallucinogens in a variety of sociocultural, medical, or ritual contexts.

[13] Summary Points:

- Studies have shown that both serotonin and glutamate receptor systems play a crucial role in the mechanisms underlying drug-induced synesthesia.
- However, the specific mechanisms underlying drug-induced synesthesia remain unknown.
- Two distinct hypotheses for how synesthesia triggered by hallucinogens in the serotonin-agonist family may occur.
- One hypothesis is that the drug-induced destabilization of thalamic projections via GABAergic neuronal circuits from sensory areas leads to a disruption of low-level, spontaneous integration of multisensory stimuli.
- This sort of integration regularly occurs when spatial and temporal attributes match.
- Destabilization of feedback loops, however, can result in incongruent experiences or binding of random thalamus activation with sensory input in a particular sensory modality.
- The second hypothesis builds on embodied cognition, cases in which visual images of external stimuli activate task-related neural regions.
- Binding processes that do not normally generate awareness become accessible to consciousness as a result of decreased attentional discrimination among incoming stimuli.
- It is plausible that both mechanisms may underlie different instances of drug-induced synesthesia.

[14, 15, 17] Titles and Legends to Table or Figures

Figure1: Contextual differences affect synesthetic experiences.

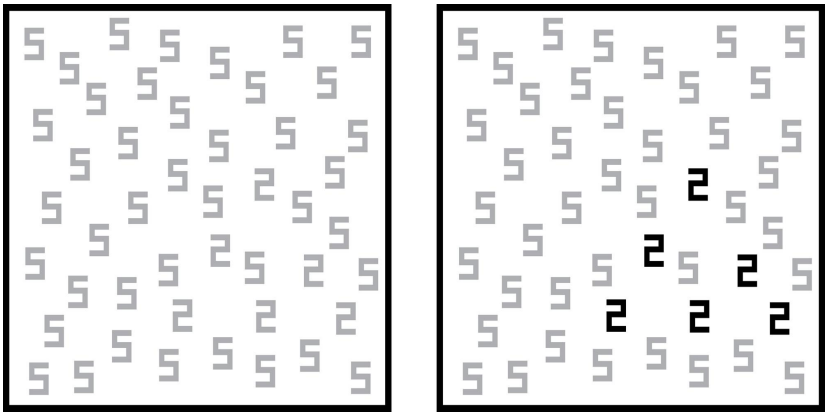
Legend to Figure 1. The number string 13 can look like the letter B when couched between A and C but as the number 13 when couched between the numbers 12 and 14. Some synesthetes will have different synesthetic experiences when viewing the number sequence in different embedding contexts (Blake et al., 2005).

Figure 2: Table used to test-retest reliability of synesthetic experience over time.

		Grapheme									
		0	1	2	3	4	5	6	7	8	9
Age (in years)	3	/	B	Y	G	P	R	Bl	W	Br	R
	4	/	B	Y	G	P	R	Bl	W	Br	R
	5	Go	B	Y	G	P	R	DBr	W	Br	R
	6	Go	B	Y	G	P	R	DBr	W	Br	R
	7	B	B	Y	G	P	R	Br	W	Br	R
	8	B	B	Y	G	P	R	Bl	W	Br	R
	9	B	B	Y	G	P	R	Bl	W	Br	R
	10	B	B	Y	G	P	R	Bl	W	Br	R
	11	B	B	Y	G	P	R	Bl	W	Br	R
	12	B	B	Y	G	P	R	Bl	W	Br	R

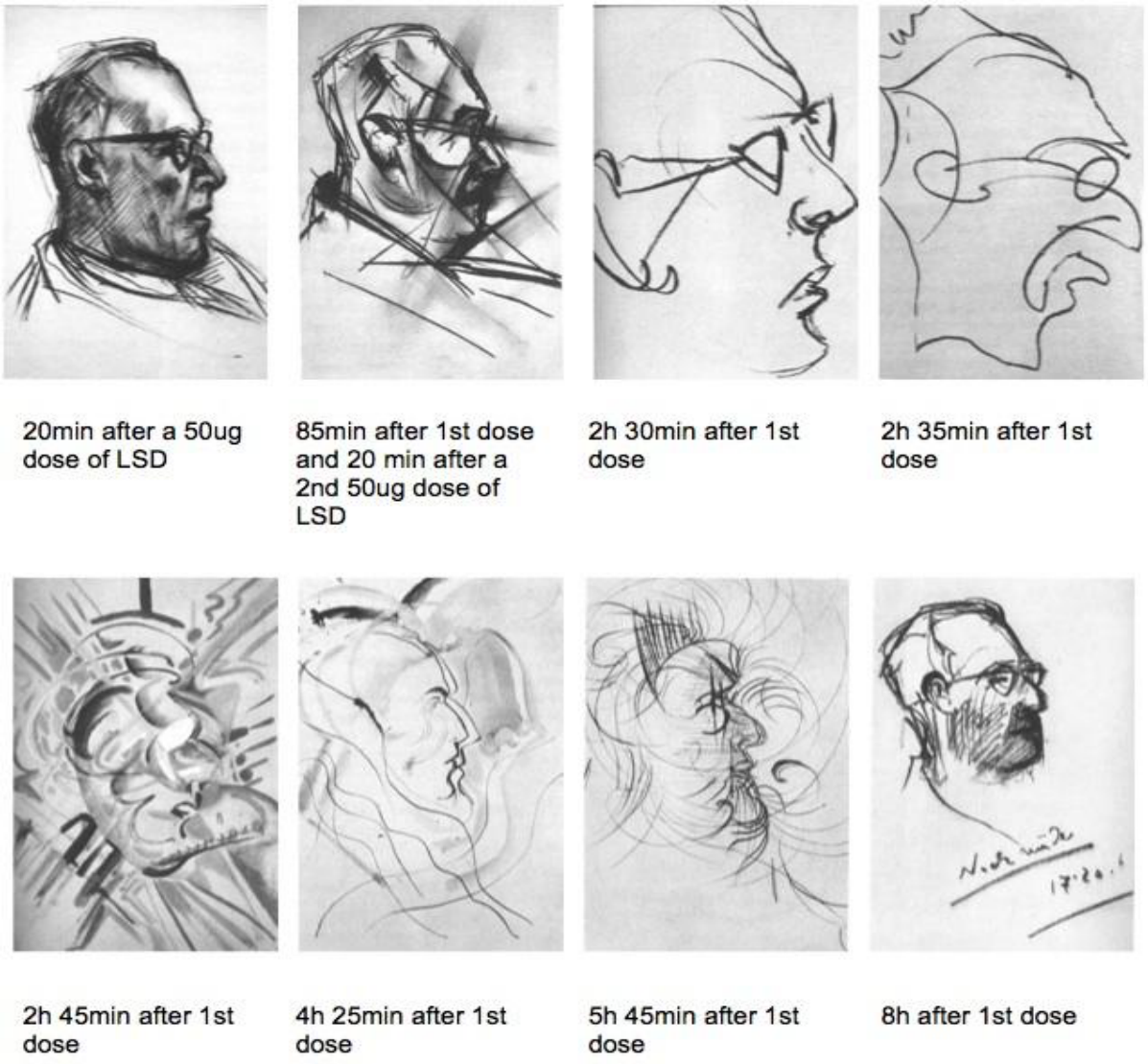
Legend to Figure 2. Example of test-retest reliability of synesthetic experience in one of our subjects with associator grapheme-color synesthesia from ages 3 to 12 (**B**lue, **Bl**ack, **Br**own, **D**ark **Br**own, **G**reen, **Go**ld, **P**urple, **R**ed, **W**hite, and **Y**ellow). The subject was tested by researchers at the Brogaard Lab for Multisensory Research, University of Miami, for our database of individuals with synesthesia.

Figure 3: Template used in stroop tests



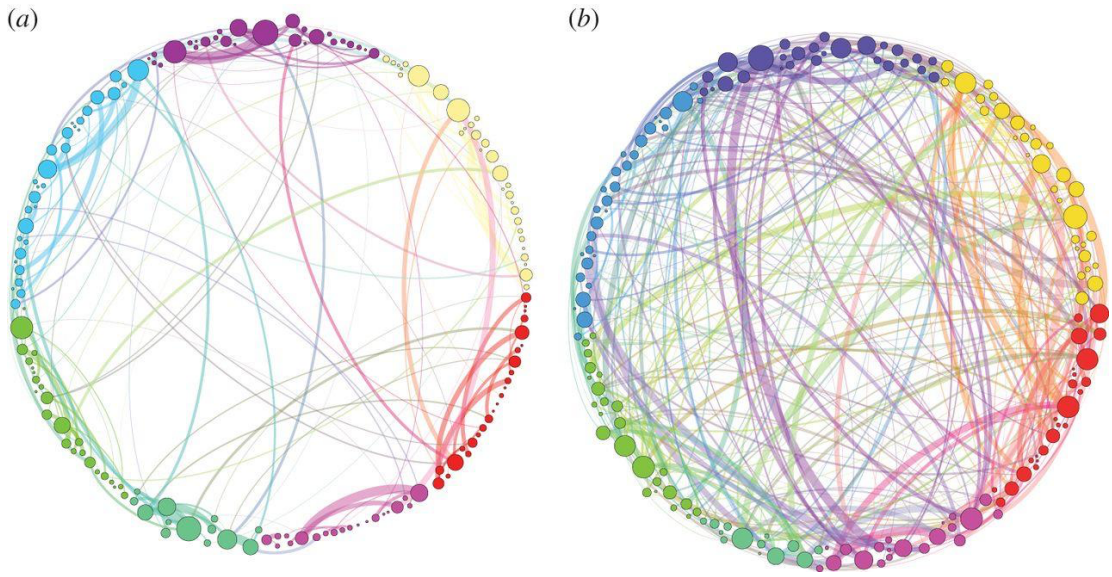
Legend Figure 3. When non-synesthetic subjects are presented with the figure on the left, it takes them several seconds to identify the hidden shape. Some grapheme-color synesthetes purportedly can immediately recognize the triangular shape because they experience the 2s and the 5s as having different colors (see Ramachandran & Hubbard, 2001b).

Figure 4: Drawings made by an artist under the influence of LSD



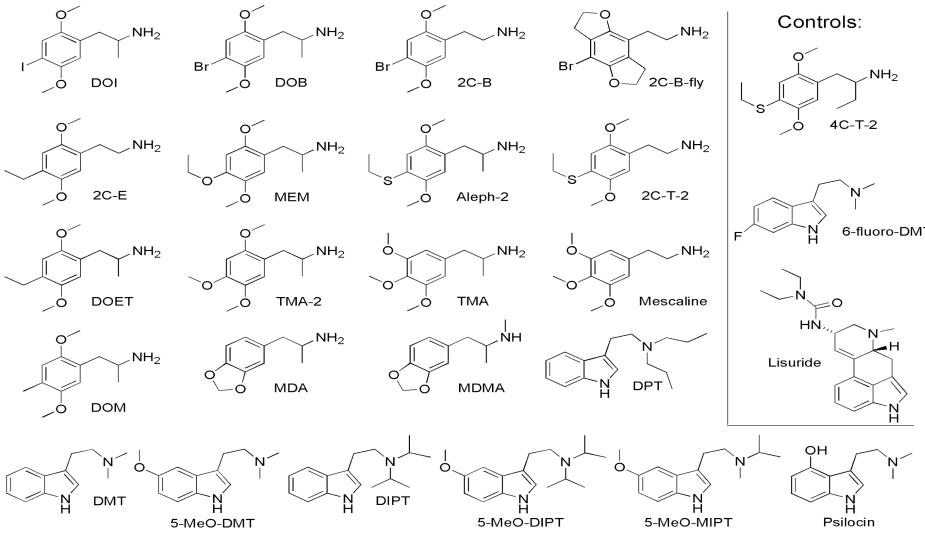
Legend to Figure 4. These drawings resulted from a test on the effects of LSD conducted by the government in the late 1950s (Bercel et al., 1956; see also https://www.youtube.com/watch?v=8ZIZtiWhnM8 Assessed on 1/31/2015).

Figure 4: A comparison of functional differences between placebo (a) and hallucinogens (b).



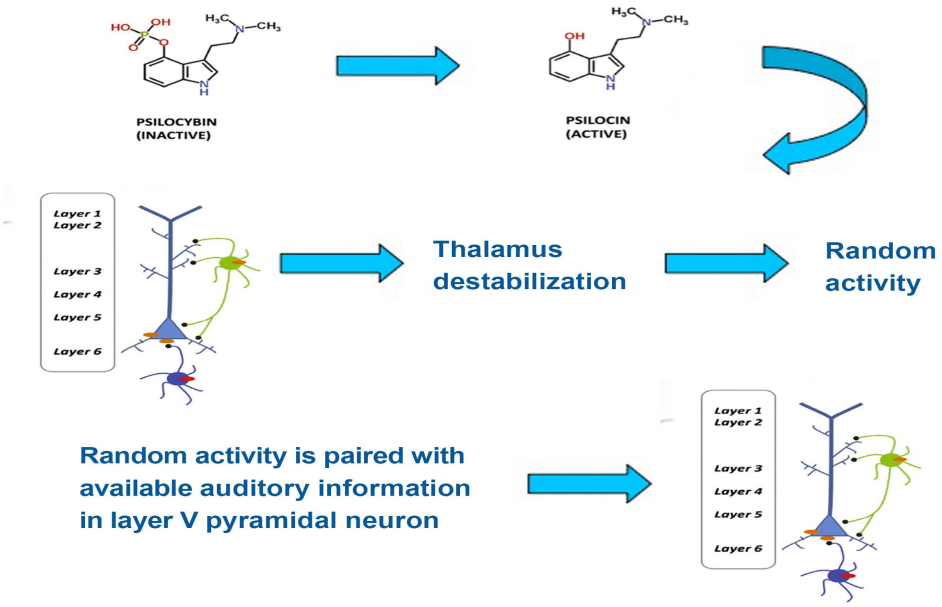
Legend to Figure 5: An illustration of the connections between neurological activity in subjects given a placebo (a) and those given psilocybin (b). From Petri et al. (2014).

Figure 6: The chemical structures of various hallucinogenic drugs.



Legend to Figure 6: These twenty-five drugs include sixteen phenylalkylamines, eight tryptamines, and one ergoline. The three control drugs on the right include one representative from each structural class, and are believed to be non-psychedelic. Adopted from Ray (2010).

Figure 7: A hypothesis of the mechanisms underlying drug-induced synesthesia.



Legend to Figure 7. Psilocin triggers a 5-HT2A excitability response in layer V pyramidal neurons and an inhibitory response in GABAergic interneurons. This leads to thalamic destabilization, which triggers random thalamic activity. The occipitally processed random activity is paired with available auditory information in layer V pyramidal neurons, which yields synesthetic experiences. Adopted from Brogaard (2013).

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Word count
6893 words (abstract, key words and references not included in word count)
7 figures 150 references
4008 words in references

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[19-21] We complied with all of these requirements.