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Publication Date

2010

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Other Times I Can Barely See: The Effects of Hallucinogens on Vision and Attention

By

Matthew John Baggott

A dissertation submitted in partial satisfaction of the
requirements for the degree of

Doctor of Philosophy

in

Neuroscience

in the

Graduate Division

of the

University of California, Berkeley

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Spring 2010

Abstract

Other Times I Can Barely See: The Effects of Hallucinogens on Vision and Attention

by

Matthew John Baggott

Doctor of Philosophy in Neuroscience

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Professor Lynn C. Robertson, Chair

In this dissertation, I used theories of serotonin to understand the effects of serotonergic hallucinogens on visual perception and attention. I began by studying hallucinatory syndromes in drug users in Chapter 1. Despite long-standing reports of prolonged or reoccurring perceptual changes in a subset of hallucinogen users, very little is known about Hallucinogen Persisting Perception Disorder (HPPD) and related visual abnormalities in hallucinogen users. I used an online questionnaire to document the prevalence, symptoms, and relationship to drug use of persisting unusual visual phenomena in hallucinogen users. 16,192 individuals viewed the information sheet, and 2,679 were included in the study. Most participants (61.7%) reported having experienced drug-free visual experiences that resembled hallucinogen effects. Probability of experiencing constant or near-constant symptoms was predicted by greater past exposure to specific hallucinogens, including lysergic acid diethylamide (LSD). Although symptoms were common, few (104, or 3.9 % of the sample) found them distressing or impairing enough to consider seeking treatment. In Chapters 2 and 3, I used three pharmacological agents to alter serotonergic functioning: 3,4-methylenedioxyamphetamine (MDA); 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'); and the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram. Chapter 2 focuses on mechanisms of hallucinations, which I investigated by measuring the perceptual effects of the hallucinogenic 5-HT_{2A}R agonist and 5-HT releaser 3,4-methylenedioxyamphetamine (MDA) in a double-blind placebo-controlled study. I found that MDA produced a significant increase in closed-eye visuals (CEVs), with considerable individual variation. Magnitude of CEVs after MDA was associated with lower performance on measures of contour integration and object recognition, supporting a hypothesized link between hallucinations and impairments in sensory or perceptual processing. Chapter 3 concerned the effects of the aforementioned serotonergic drugs on attention to threat-related stimuli. The serotonergic system appears important for evaluation of social stimuli and may modulate amygdala sensitivity to threat-related stimuli. Hallucinogens and related serotonergic drugs vary in their ability to release 5-HT, but no studies have measured how these drugs affect attentional biases for emotional stimuli. In this chapter, I describe two double-blind placebo-controlled experiments on the effects of the serotonergic drugs 3,4-methylenedioxyamphetamine

(MDA) and 3,4-methylenedioxymethamphetamine (MDMA) on attention to emotional stimuli. Using a dot-probe task, I found preliminary evidence that MDA and MDMA may modify processing of threat-related stimuli. These effects appear unrelated to state anxiety. In contrast, I did not detect significant effects of the selective serotonin reuptake inhibitor (SSRI) citalopram. Further research with these understudied drugs may clarify the role of serotonin in the brain.

ACKNOWLEDGEMENTS

The tea is poured and the water's transformation completed. In savoring this moment, I wish to honor the many hands that brought it about. The tea did not make itself. Years ago, careful hands selected clear and eager water, bringing it to the kettle to be heated. Experienced ears knew when the water was the right temperature; not every kettle sings, but the murmur of boiling water always becomes more consistent, more confident. And then the water was poured into the teapot to absorb alone what the leaves had to offer. The pot was dark but each hand-picked tea leaf was a scroll, a message from distant lands. Eventually the strange teapot became comfortable and there was a danger of the tea steeping too long, but watchful eyes were always close. And now the water is surprised to find it has somehow improbably become tea.

There are many people to acknowledge. My first scientific mentors, Lewis Seiden and Reese Jones, filtered the water and kept it clear. My fellow students—especially Elena Allen, Gautam Agarwal, Andre Bastos, Annaliese Beery, Ryan Canolty, Cathrine Dam, Ayelet Landau, Mike Esterman, and Brian Pasley—made the heat seem cozy, almost like a sauna. The folks at California Pacific Medical Center Research Institute—especially John Mendelson, Gantt Galloway, Jeremy Coyle, Ryne Didier, Keith Flower, Kathleen Garrison, Danielle Hubbard, Juan Carlos Lopez, and Jennifer Seigrist—kept the fuel coming and waited patiently. My qualifying exam committee members—Lynn Robertson, Dennis Levi, Stephen Palmer, and Robert Knight—knew when the water was ready for the leaves. My dissertation committee—Lynn Robertson, Dennis Levi, David Presti, and Michael Silver—made certain the tea was made right, had the right leaves, and did not oversteep. Most of all, my family, friends, and loved ones—especially Jaime Yassif, Nori Heikkinen, Mike Burton, Emily Clough, Travis Mowbray, Katherine Bonson, and Alana Conner—kept me going through the darkest years in the teapot, when I could barely see. I hope you all know how important you were to my success.

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INTRODUCTION

In 1948, Rapport and colleagues [1] isolated from beef serum a compound that induced vasoconstriction and altered vascular muscular tone. They named it “serotonin” to indicate its origin and effects. This achievement is particularly impressive when one considers that blood contains only 0.05-0.5 ug/ml serotonin, mostly in platelets [3]. The work to isolate and identify the compound required approximately “900 liters of serum collected from almost two tons of beef blood” [4]. Within a few years, serotonin’s structure had been identified as 5-hydroxytryptamine (5-HT), identical to the compound that Erspamer and Vialli [5] had derived from the enterochromaffin cells of the gut and named “enteramine”. About nine of the body’s 10 mg of 5-HT are located in mucous membranes of the gastrointestinal system [6]. Small amounts of 5-HT are also found in the central nervous system (CNS), particularly the hypothalamus and limbic system [7, 8]. The relative amount of 5-HT in CNS is small – only about 1–2% of the body’s total. Nonetheless, 5-HT is now recognized to play an important, if mysterious, role in CNS function.

Historically, research with psychoactive drugs has been important in advancing understanding of 5-HT in the CNS. The importance of 5-HT in the CNS was first hinted at when the powerful hallucinogen lysergic acid diethylamide (LSD) was shown to antagonize the effects of 5-HT in smooth muscle preparations [9, 10]. Soon thereafter, Pletscher et al. [11] demonstrated that the antipsychotic drug reserpine reduced intestinal 5-HT concentrations. These findings provided tantalizing evidence of what is now a well-established fact: 5-HT plays an important role in psychosis and other mental illness. From our modern perspective, it is difficult to appreciate how radical it once was to suggest that mental illness might have a biological basis, let alone a basis involving a simple molecule like 5-HT [4, 12]. Since the 1950s, thousands of studies have explored the role of 5-HT in mental illness and, more generally, the CNS.

Despite these decades of focused research, 5-HT remains mysterious. In a prescient 1956 editorial in *Circulation*, McCubbin and Page [13] suggested that 5-HT would guarantee “tenure for the pharmacologist.” Over 50 years later, it is still unclear exactly what roles 5-HT plays in the brain. While 5-HT remains maddeningly elusive, there are also ample reasons to study it. From a clinical perspective, drugs with serotonergic effects are important for treating depression, anxiety disorders, and psychosis. From a broader perspective, serotonergic drugs with hallucinogenic or MDMA-like activity have the potential to reliably and, under proper circumstances, safely produce transformative experiences that are similar or identical to peak or mystical ones [14, 15]. Understanding these effects may reveal something fundamental about the human condition to neuroscience while potentially reducing suffering relating to both adverse drug effects and the human condition.

In this dissertation, I explore the role of 5-HT in hallucinations, visual perception, and attention. I begin by studying hallucinatory syndromes in drug users in Chapter 1. Serotonergic drugs are widely consumed. For example, an annual nationwide representative survey estimated that 14.8% of young adults (Ages 19–28) have used hallucinogens and 13.1% have used ‘Ecstasy’ [16]. Thus, hallucinatory syndromes in

drug users may have broad public health implications. In Chapters 2 and 3, I use three pharmacological agents to alter serotonergic functioning: 3,4-methylenedioxyamphetamine (MDA); 3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’); and the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram. Chapter 2 focuses on mechanisms of hallucinations, while Chapter 3 is dedicated to the effects of the aforementioned drugs on attention to threat-related stimuli.

In the remainder of this introduction, I provide a background review of the neuropharmacology of 5-HT and these three drugs, including an integrative summary of theories of 5-HT functioning in the brain. I hypothesize that an important function of 5-HT is adjusting the sensitivity of a behavioral inhibition or withdrawal system. This theory allows us to make predictions about the effects of serotonergic drugs on perception and attention. In terms of perception, I predict that the serotonergic hallucinogen MDA will induce visual pseudo-hallucinations (i.e., false perceptions that are not taken for reality) and that, depending on the mechanism (which can be hypothesized to include general perceptual impairments, cognitive alterations, and/or increased cortical excitation), these changes will be accompanied by alterations in contour integration, object perception, and/or strength of the tilt illusions, respectively. I test these predictions in Chapter 2. In terms of attention, I predict that 5-HT releasers such as MDA and MDMA should impair the attentional effects of threat-related stimuli. Although some studies have suggested that evaluation of social and emotional stimuli may be altered by MDMA [17, 18], no studies to date have evaluated potential attentional effects of MDMA using social or emotional stimuli, which I attempt in Chapter 3. The following review provides a more detailed basis for my predictions.

BACKGROUND

The neuropharmacology of serotonin

Serotonin in the brain. Using the Falck–Hillarp technique of histofluorescence, Dahlstrom & Fuxe [19] identified nine different 5-HT-containing cell groups in the CNS, designating them B1–B9. These cell groups originate mostly in the raphe nuclei, which Taber et al. [20] had defined based on cell-body structural characteristics and organization.

The largest group of serotonergic cells, group B7, is conventionally grouped with the neighboring cells of B6 as the dorsal raphe nucleus. Estimates of the proportion of serotonergic neurons in groups B6 and B7 combined (the dorsal raphe) vary from one to two thirds [21]. (Thus, not all raphe neurons are serotonergic.) Groups B5 and B8 correspond to the median raphe nucleus. Group B9, part of the ventrolateral tegmentum of the pons and midbrain, forms a lateral extension of the median raphe and, therefore, is not considered one of the midline raphe nuclei. Ascending serotonergic projections to the forebrain primarily arise from these groups [22, 23]. The remaining, more caudal, raphe nuclei – groups B1–B4 – contain a smaller number of serotonergic cells that project within the brainstem or to the spinal cord.

Serotonin electrophysiology. Aghajanian and Vandermaelen [24] first characterized the electrophysiological properties of serotonergic dorsal raphe cells with *in vivo* intracellular recording and neurochemical verification. Following from this and subsequent works, 5-HT-containing neurons have been classically described as either silent or displaying a slow, rhythmic firing pattern (0.5–2.5 Hz), in which a long-duration action potential (approximately 1.8 ms) is followed by a large, slow afterhyperpolarization potential (amplitude=10–20 mV, 200–800 ms) and gradual interspike depolarization [24–27]. This would seem to suggest that 5-HT might play some coordinating function in the brain rather than encoding time-varying information.

However, in the last ten years, research has produced convincing reports of a confusing diversity of nonclassical serotonergic behaviors. Kirby and colleagues [28] measured membrane properties and receptor-mediated responses of rat dorsal raphe nucleus neurons in a slice preparation and determined that many *nonserotonergic* cells fit the classic properties of serotonergic dorsal raphe nucleus neurons. In their study, serotonergic cells (distinguished with immunohistochemistry) were discernible by the gradual initial phase of the afterhyperpolarization potential and shorter membrane time constant compared to nonserotonergic cells. Urbain et al. [29] recently described the diversity of electrophysiological properties of dorsal raphe cells across the sleep-wake cycle in rats by the extracellular recording of a large sample of single units (n=770). They identified two major types of cells: those with broad, mostly positive spike waveforms, and those with the initial positive depolarization being followed by a similarly sized negative deflection in their waveforms and a large distribution of spike durations (0.6–3.2 ms). Furthermore, many cells continued to fire during sleep compared with wakefulness, including paradoxical sleep when most raphe cells are silent.

Serotonergic and nonserotonergic cells are also pharmacologically diverse, with subpopulations of both serotonergic and nonserotonergic neurons responding with outward (i.e., inhibitory) and inward (i.e., excitatory) currents when either 5-HT or selective 5-HT_{1A} receptor or 5-HT_{2A/C} receptor ligands are applied [30]. Thus, serotonergic and nonserotonergic neurons in the dorsal raphe are more heterogeneous in electrophysiology and pharmacology than previously realized, suggesting serotonin may be engaged in complex signaling.

Serotonin synthesis, release, and diffusion. The serotonin precursor l-tryptophan competes with other large, neutral, and branched-chain amino acids for active transport into the brain. Consequently, dietary manipulations that decrease the relative ratio of l-tryptophan to other competing amino acids can cause acute depletions of 5-HT in the brain. For example, estimates using positron emission tomography and alpha-methyl-[¹¹C]-tryptophan indicate that the 5-HT synthesis rate is reduced by ~87% and ~97% in healthy men and women, respectively, five hours after intake of a low tryptophan amino acid mixture [31]. It has been suggested that tryptophan's sensitivity to dietary depletion acts as a physiological signal of inadequate resources due to famine or sickness [32]. Researchers have used acute tryptophan depletion via oral amino-acid loading as a tool to probe the effects of decreasing serotonergic functioning in humans.

Once transported across the blood brain barrier, l-tryptophan is synthesized into 5-HT within serotonergic neurons, with tryptophan hydroxylase as the rate-limiting enzyme. Newly formed 5-HT is stored in synaptic vesicles that protect 5-HT from degradation by monoamine oxidase (MAO). Released 5-HT can be removed from the synapse by high-affinity, presynaptic, sodium-dependent 5-HT transporters (serotonin transporter, or SERT; aka 5-HTT). It can also be metabolized by the MAO subtype MAO-A to 5-hydroxy-indolacetic acid (5-HIAA).

Studies in the rat indicate that the action of 5-HT is often not restricted to the synaptic cleft. Instead, it can frequently diffuse to remote receptor sites (called volume, diffuse, or paracrine transmission, in contrast to hard-wired neurotransmission). Such volume neurotransmission appears to dominate for serotonin in the rat dorsal raphe, cerebral cortex, and hippocampus [33]. There, immunogold electron microscopic studies indicate that SERT is mainly located on the plasma membrane of axons away from well-defined postsynaptic densities [34]. In contrast, the medial amygdaloid nucleus of the macaque shows a correspondence of SERT- and serotonin-immunoreactivity, indicating that classical hard-wired neurotransmission is likely dominant here [35].

Serotonin receptor overview. Peroutka and Snyder [36] confirmed early evidence [37] of more than one 5-HT binding site in the brain when they determined that binding of different radio-labeled compounds to 5-HT receptors (5-HTR) in the rat frontal cortex depended on the compound. Today, we recognize seven families of 5-HTR (5-HT₁–7 receptors, or 5-HT₁–7R), and evidence exists of at least 14 subtypes in mammals [4, 38]. With the exception of the ligand-gated ion channel 5-HT₃ receptor, all 5-HTR are G-protein-coupled. Below, I briefly describe the characteristics of 5-HT₁R and 5-HT₂R, two families that appear to play an important role in the effects of hallucinogens.

5-HT₁R and 5-HT₂R have opposite effects on neuronal excitation: 5-HT₁R stimulation hyperpolarizes, while 5-HT₂R stimulation depolarizes. Because 5-HT has very different affinities at 5-HT₁R and 5-HT₂R (nanomolar and low micromolar, respectively), the 5-HT₁R may play a more dominant role in modulating processing. However, microdialysis studies of the frontal cortex suggest synaptic concentrations of 5-HT can be sufficient to stimulate both receptor types [39].

The two subtypes of the 5-HT₁R – 5-HT_{1A}R and 5-HT_{1B}R – act as autoreceptors by regulating the firing rate of serotonergic neurons [40, 41]. Both subtypes are also stimulated by 5-HT through a volume transmission process [42]. The 5-HT_{1A}R is presynaptic in raphe nuclei but postsynaptic in limbic structures of the forebrain, where it inhibits pyramidal cell firing (e.g. [43, 44]). The 5-HT_{1B}R can be found on the terminals of serotonergic cells or on nonserotonergic cells, where it acts as a heteroreceptor inhibiting the release of different neurotransmitters, including acetylcholine and gamma-aminobutyric acid (GABA) [45-47].

The 5-HT₂R family has three subtypes – 5-HT_{2A}R, 5-HT_{2B}R and 5-HT_{2C}R – which are generally similar, having 80% sequence identity in their transmembrane domains [4]. The 5-HT_{2B}R is distributed mainly in the periphery, including the heart, where prolonged exposure to serotonergic drugs may lead to toxic effects via a 5-HT_{2B}R mechanism [48].

The 5-HT₂CR, in contrast, is widely distributed in the CNS, and is possibly the most numerous serotonin receptor [49]. The 5-HT₂AR is primarily postsynaptic [50] and has higher densities in temporal, frontal, parietal, occipital, and cingulate cortices and lower densities in subcortical areas and basal ganglia [51, 52]. In the thalamus, the 5-HT₂AR is primarily found in sensory and “nonspecific” nuclei but not in motor nuclei [53]. In the cortex, 5-HT₂A receptors are densest in the apical dendrites and somata of pyramidal neurons. However, they also are present on cholinergic neurons [54] and the large- and medium-sized parvalbumin and calbindin-containing GABA-ergic interneurons [55, 56]; they have additionally been detected on glial cells [57, 58]. Blue et al. [59] noted that the laminar distribution of 5-HT₂AR-binding in the rat frontal cortex matched serotonergic innervation from the dorsal raphe. Double-labeling immunocytochemistry in forebrain regions shows a lack of association between 5-HT₂AR and serotonergic varicosities, providing evidence that volume neurotransmission involves this receptor [60]. The 5-HT₂AR can couple independently to phospholipase C (PLC), phospholipase D, and phospholipase A₂ (PLA₂). The relative efficacy of agonists for these pathways varies independently, a concept known as agonist-directed trafficking, or functional selectivity [61].

Theories of the function of 5-HT in the brain

In this section, I review and attempt to synthesize theories of 5-HT. 5-HT plays multiple roles in the brain based on its neuroanatomy and the different time scales of its effects. Phasic 5-HT release is hypothesized to signal aversive outcomes, while tonic 5-HT release coordinates neural activity more globally, potentially as part of a global withdrawal system. In advancing this hypothesis, I make explicit links between research on dopamine and serotonin and theories of approach and withdrawal systems.

There is a long tradition of arguing that two distinct appetitive and aversive motive systems underlie behavior, affect, and personality. The first is often called a behavioral approach system, the other a behavioral inhibition (or withdrawal) system [62-65]. While many theories of affect implicitly or explicitly link positive valence to one system and negative valence to the other, Carver [66] has argued that both systems can produce positive and negative valence when a process of either approach or avoidance is doing better or worse than expected. Specifically, negatively valenced affect of the approach system includes anger and sadness, while negatively valenced affect of the avoidance system involves anxiety.

A conceptually pleasing possibility is that dopamine and 5-HT may play parallel roles in the behavioral approach and inhibition systems. Phasic dopamine release signals reward- or approach-prediction errors, while tonic dopamine regulates the stability of different approach processes [67-69]. Correspondingly, I speculate that phasic 5-HT release signals punishment- or threat-prediction errors, while tonic 5-HT regulates the stability of different withdrawal processes. Similar to the theory of dopamine advanced by Grace and colleagues [70, 71], tonic levels of 5-HT may regulate the gain of phasic signaling, with high tonic levels decreasing the effectiveness of phasic release by receptor desensitization and internalization as well as stimulation of autoreceptors on neurons participating in the phasic signal. One hypothesis that follows from the link between 5-HT and a withdrawal

system is that dysfunctional serotonergic signaling could lead to user anxiety and fear (high phasic signaling), or relief and calmness (high tonic levels). This suggests that drugs like MDA and MDMA, which release 5-HT by a mechanism independent of cell firing and dramatically increase tonic 5-HT, should decrease this hypothesized phasic 5-HT signal.

While this theory is a novel synthesis of the literature, it is consistent with other theories of 5-HT. Theories of 5-HT have consistently linked it to inhibition and processing of aversive stimuli. The hypothesis that 5-HT is involved in behavioral inhibition was developed by Soubrié [72] and recasts the reduction of anxiety associated with serotonergic manipulations as the removal of behavioral suppression. Although derived primarily from animal research, this theory is consistent with the known link between 5-HT and impulse-control disorders in humans. However, contrary to this theory, studies in humans and animals have not consistently linked serotonergic manipulations with changes in general motor-response inhibition in tasks such as the go/no-go [73, 74] or the stop-signal reaction time task [75, 76].¹ Furthermore, an important recent paper by Crockett et al. [77] used acute tryptophan depletion and a modified go/no-go task to demonstrate that manipulating 5-HT selectively altered adversely motivated behavioral inhibition rather than more general motor-response inhibition. Tops et al. [78] have proposed a primitive withdrawal-drive hypothesis of 5-HT function, suggesting that facilitation of withdrawal may be a common denominator to the proposed functions of the two main raphe nuclei.

In an influential and nuanced theory, Deakin and colleagues [79-81] proposed that 5-HT disengages stimuli from their emotional consequences, with different projections of serotonergic neurons serving different functions. Median raphe 5-HT cells suppress awareness of adverse memories and contexts through their projections to the hippocampus and cingulate gyrus; dorsal raphe 5-HT cells, in contrast, mediate avoidance of threats via projections to the amygdala. Thus, the association of 5-HT with different pathological symptoms was explained by differential impairment of these distinct systems. Cools, Roberts, and Robbins [82] also theorize that subcortical and cortical 5-HT have different roles. At the subcortical level, serotonergic activity provides an aversive motivational process opposed to that which is mediated by dopamine activity. Serotonergic projections to the orbitofrontal cortex (OFC) facilitate inhibitory control of subcortical regulation of emotional processing and behavioral output.

Dayan and colleagues [83] have suggested that phasic 5-HT release may signal a prediction error in aversive outcomes. This theory is based partly on theoretical grounds relating to the utility of such a prediction error signal, rather than physiological evidence. While there are substantial data supporting the theory that 5-HT modulates processing of aversive outcomes [82], no one has directly measured a phasic 5-HT response to an aversive outcome. If this error signal does exist, the amygdala may be particularly well-

¹ These tasks assess motor inhibition by measuring participants' ability to withhold response when they receive an infrequent signal during a task that otherwise requires rapid responses to frequent stimuli.

suited for implementing this function, for two reasons. First, neuroimaging studies provide evidence that functional circuits including the amygdala and prefrontal cortex rapidly encode the presence of threat-related stimuli [84-86]. Second, in contrast to its behavior in the rest of the brain, 5-HT does not appear to use volume transmission in the amygdala [35] and can thus influence amygdala functioning with high spatial specificity. In other brain areas, the lack of 5-HT transporters in the synapse allows 5-HT to diffuse and modify the functioning of cells over a greater area, potentially coordinating and shifting the state of neuronal networks.

Mechanisms of serotonergic hallucinogens

In light of the links between 5-HT and inhibition, an obvious question is why do serotonergic hallucinogens have the effects that they do. Why would perturbing a neurotransmitter system that affects inhibition and anxiety cause visual distortions and feelings of mystical insight? A partial explanation is a system that adjusts threat-sensitivity might also adjust perceptual systems to increase ability to rapidly detect these threats. However, science has no definitive explanation for why serotonergic hallucinogens cause hallucinations. In Chapter 2, I discuss causes of hallucinations from a more general non-pharmacological perspective. One hypothesis covered is that serotonergic hallucinogens increase excitation, leading to the formation of a Turing-instability and subsequent spontaneous pattern formation [87]. Here, I review mechanisms of serotonergic hallucinogens from a pharmacological perspective.

As discussed earlier, 5-HT acts as a neuromodulatory signal throughout much of the brain, likely signaling global state. Yet it also alters the response properties of sensory neurons in surprisingly specific ways: it potentially adjusts gain control of neurons [88] and changes the balance between both within-layer and between-layer cortical communication [89] and between ascending and descending projections [90]. As reviewed in this section, hallucinogens stimulate the 5-HT_{2A}R, which in turn alters cortical network dynamics. Accordingly, the hypothesized hallucinogen-induced increase in excitation appears possible, although the term ‘excitation’ may be a gloss, simplifying a complex instability in network dynamics.

A simplified but still hopefully useful model is to consider the difference between stimulation of 5-HT receptors by 5-HT and stimulation by serotonergic 5-HT_{2A}R agonist hallucinogens. When 5-HT_{2A}R is normally stimulated by 5-HT, there is also stimulation of inhibitory receptors, including 5-HT_{1A}R. Because 5-HT_{1A}R are more readily stimulated by 5-HT (i.e. 5-HT binds with higher affinity), these receptors may exert a surround inhibition effect around an area where 5-HT is released. In contrast, when a 5-HT_{2A}R agonist hallucinogen is given, there will be excitation without this accompanying inhibition, which would be expected to profoundly alter network dynamics.

Role of the 5-HT_{2A}R in hallucinogen effects. Stimulation of several receptors, including the 5-HT_{1A}R, 5-HT_{1B}R, 5-HT_{2C}R, 5-HT_{5A}R, and dopamine D₂R, can contribute to the psychoactive effects of hallucinogens [91]. Nonetheless, the 5-HT_{2A}R appears to be key in the production of hallucinogen effects. Affinity for the 5-HT_{2A}R is highly correlated with hallucinogenic activity in drug-discrimination studies [92, 93], and

inactivating the 5-HT_{2A}R with pharmacological or genetic techniques blocks the behavioral and self-reported effects of hallucinogens in humans and nonhumans [94-96].

Electrophysiological and microdialysis techniques indicate that hallucinogens activate 5-HT_{2A}R located on presynaptic terminals and increase glutamate release onto layer V pyramidal cells [97, 98]. In the past, some researchers have proposed that hallucinogens activate presynaptic cortical 5-HT_{2A}R expressed in thalamocortical terminals [99, 100], and others have argued that these drugs directly target postsynaptic cortical 5-HT_{2A}R [101-105]. Recent knockout and tissue-specific rescue studies suggest that cortical 5-HT_{2A} receptors are sufficient to induce the characteristic head-twitch effect of hallucinogens in mice [106], supporting a key role for 5-HT_{2A}R on cortical neurons.

Stimulation of the 5-HT_{2A}R produces an alteration in cortical network dynamics. After many years studying hallucinogen-induced glutamate release (measured as an “asynchronous” late excitatory postsynaptic current), Aghajanian [107] concluded that it comprises mixed inhibitory and excitatory components and reflects recurrent network activity. Lambe and Aghajanian [108] describe this activity as resembling the “up states” that result from sustained activity in balanced excitatory and inhibitory recurrent networks [109]. Thus, hallucinogens induce recurrent network activity. This recurrent activity seems consistent with the hypothesized increase in excitability predicted by Ermentrout-Cowan models of geometric hallucination [87], which I review in Chapter 2.

Contributions of other serotonergic receptors in the sensory effects of hallucinogens.

Effects of 5-HT_{2A}R-stimulation in the frontal cortex are hypothesized to be important for the cognitive effects of hallucinogens [110], and the evidence reviewed above corresponds with the theory that recurrent network activity in the occipital cortex might contribute to visual hallucinations. However, only some hallucinogens produce profound visual alterations; many appear to have primarily cognitive effects, with fewer perceptual changes. Why, then, are some drugs more “visual” than others?

Different efficacies at 5-HT_{1A}R [111] or 5-HT_{1B}R [112] may contribute to such changes in sensory processing. The 5-HT_{1B}R, in particular, has been reported to modulate sensory transmission, including retinocollicular [113], thalamocortical [114], and retino-suprachiasmatic nuclear [115] pathways (the latter probably involving circadian rhythms rather than visual information). The primary visual area (V1) of macaques has a striking enrichment of 5-HT_{1B}R mRNA, and to a lesser extent, of 5-HT_{2A}R mRNA compared to examined temporal, somatosensory, motor, and frontal regions [112]. Both receptors are concentrated in the geniculorecipient layers IVA and IVC, where they are often co-localized on neurons. *In vivo* electrophysiological studies of V1 neurons find modulatory effects of agonists at both receptors [101]. 5-HT_{1B}R stimulation with the 5-HT_{1B} receptor agonist CP93129 displays firing-rate-dependent modulation on cells, with facilitation often seen with higher firing rates and suppression with lower rates. Such firing-rate-dependent effects are consistent with earlier *in vitro* studies of slices containing the ventral posteromedial nucleus of the thalamus and the somatosensory cortex [114] or the optic tract and the LGN [116].

The 5-HT_{1B}R may also disinhibit network activity via receptors on a subset of GABA-ergic neurons. 5-HT_{1B}R stimulation in the inferior colliculus (IC) – the principal midbrain nucleus of the auditory pathway – causes not only increased sound-evoked responses, but also, in some neurons, altered facilitatory or inhibitory responses from tones at frequencies that are an octave or more from the neurons' excitatory curves [117, 118]. Although it occurs in a very different brain region than the occipital cortex, this phenomenon shows that, in principal, serotonergic manipulations and resulting changes in network activity can alter lateral interactions within a brain region.

Possible hallucinogen-induced alterations in thalamic functioning. One early theory hypothesized that the drug LSD induces hallucinations by changing how the dorsal lateral geniculate nucleus (LGN) of the thalamus responds to visual stimulation [119, 120]. Increased variability in LGN output, for example, might cause visual distortions; a decrease in spontaneous LGN activity, in contrast, could lead to disinhibition of cortical cells (thought to be tonically inhibited by LGN afferents synapsing on basket cells [121]), which in turn could cause visual phenomena in the absence of retinal stimulation. However, this theory relies on electrophysiological phenomena that seem relatively brief and require large concentrations of the drug. Furthermore, these findings have typically been observed in anesthetized animals, and thus have unclear relevance to the understanding of hallucinogen effects in humans. Nonetheless, a role for changes in thalamic information processing – particularly at very high doses of hallucinogens – cannot be excluded.

Early evidence for this theory begins with Evarts et al. [120], who found that intra-carotid injection of 30 ug/kg LSD in cats decreased the postsynaptic lateral geniculate local field response to optic nerve stimulation by 30–100%. (For comparison, a typical human dose of LSD is proportionally much lower, approximately 1–2 ug/kg oral.) Suspicion of a thalamic mechanism for LSD effects increased when Evarts et al. [120] additionally reported that even when given at higher doses, LSD did not affect the response of the cortex to optic radiation stimulation, and had only a modest depressant effect on the flash-evoked response of the optic tract (in doses of 2.5 mg/kg). Bishop et al. [122] then studied the effects of LSD on pre- and postsynaptic components of the dorsal LGN-evoked response. They found that LSD, in intravenous doses of 5 ug to 1 mg, reduced postsynaptic spiking in the LGN of the anesthetized cat without changing presynaptic geniculate response to optic nerve stimulation. This suggested that the drug was interfering with LGN activity. Curtis and Davis [123] and Phillis et al. [124, 125] applied LSD to LGN neurons of cats using iontophoresis, with resulting depression of spontaneous and evoked activity.

In seeming conflict with the theory that LSD decreases the fidelity of transfer of visual information through the thalamus are several studies reporting *increased* response to visual stimulation after *lower doses* of LSD in *unanesthetized* animals. For example, Purpura [126, 127] administered LSD to cats (paralyzed with succinylcholine) and found that doses of 2–5 ug/kg LSD increased the electrocortical response to auditory and visual stimuli, while higher doses (30–60 ug/kg) depressed the auditory but not visual response, which remained increased. Koella and Wells [128] studied the effects of LSD on

optically evoked potentials in the cortex of unanesthetized rabbits and found that lower doses of the drug modestly enhanced evoked potentials while reducing latency and variability, with changes lasting 5 or more hours. Similarly, Bradley and Key [129] reported that 1–20 ug/kg of LSD decreased auditory thresholds and antagonized habituation responses in cats. Reviewing the literature in 1972, Aghajanian concluded that:

It is clear, however, that LSD does not consistently have a depressant effect on evoked responses as might have been concluded from the early studies. In fact, with few exceptions, in unanesthetized animals LSD generally enhances or has no effect on evoked responses. [130]

Thus, lower doses that more closely resemble those taken by humans tend to result in *increased* neural responses to stimulation.

Hallucinogen effects on the eye. It also bears mentioning that visual phenomena likely depend in part on the hallucinogen's effects on the eye itself, including changes in pupil size and retinal functioning. Although noted in the first case of LSD inebriation [131], the robust pupil dilation produced by LSD seems to have first been measured by Isbell and colleagues [132]. This mydriatic effect would likely increase the effects of visual stimuli.

Hallucinogens likely also affect retinal functioning. Serotonergic receptors are found in the retina, and there is evidence of direct pathways between the primate retina and the dorsal raphe nucleus [133]. Immunoreactivity for the 5-HT_{2A}R, the receptor most implicated in hallucinogen effects, has been reported on the terminals of photoreceptor and rod bipolar cells in the rabbit [134]. In addition, green fluorescent protein was found in cone bipolar cells of transgenic mice modified to express GFP-labeled 5-HT_{2A}R [135]. However, animal studies of the effects of LSD on the retina have produced conflicting findings [136–138], possibly owing to the very broad range of drug concentrations used.

Subsequent clinical studies have detected effects of LSD in the human retina. Although Jacobsen and Gestring [139] reported no electroretinogram (ERG) changes in a single individual who did not report hallucinations after receiving a low dose of LSD (50 ug), Ostfeld and colleagues [140–143] detected changes in both the ERG and dark adaptation curves of individuals receiving hallucinogenic (75–100 ug) doses of LSD. In contrast, significant changes were not elicited by a lower nonhallucinogenic (25 ug) dose of LSD. To reduce the influence of pupil size changes, eyes were dilated with cyclopentolate hydrochloride. ERG measurements showed an increase in the scotopic *b* wave amplitude. The dark adaptation curve, whose characteristic shape reflects time-dependent changes in rod and cone functioning, showed no effects from the non-hallucinogenic dose; however, the higher dose elevated the rod threshold by 0.4 to 0.7 log units and delayed the rod-cone break by about 3 minutes. Both findings are consistent with rods becoming less sensitive, or adapting more slowly, to changes in luminance.

Pharmacology of MDA, MDMA, and citalopram

In the experiments described in this thesis, I use three pharmacological agents to alter extracellular levels of 5-HT: 3,4-methylenedioxyamphetamine (MDA); 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'); and the antidepressant citalopram (U.S. tradename Celexa).

Pharmacology of 3,4-Methylenedioxyamphetamine (MDA). MDA is a psychoactive phenethylamine that stimulates 5-HT_{2A}R receptors and releases 5-HT by interacting with the SERT. From a pharmacological point of view, therefore, it would be predicted to have mixed hallucinogen and 5-HT-releasing effects. Indeed, Alles [144], who first studied MDA in self-experiments, reported experiencing hallucinatory visual percepts of smoke rings, while subsequent researchers have emphasized the apparently MDMA-like emotional effects of MDA [145-147]. Nichols, who coauthored the first report of MDMA effects in humans [148] and has studied hallucinogens extensively (e.g., [4, 91, 149, 150]), classifies MDA as a hallucinogen on pharmacological grounds [151]. However, MDA has not been studied in controlled trials in over 30 years. Accordingly, little is known of the cognitive effects of MDA compared to MDMA (which I review next).

Though first synthesized in 1910, MDA was not studied in humans until the 1940s. It was apparently not used nonmedically until the 1960s, when it became known as "the love drug" [152]. Illicit use has continued since then, though with a lower prevalence than illicit use of MDMA. Despite MDA being considered an obscure compound today, some of what is sold as "Ecstasy" contains MDA instead of MDMA. In a sample of 107 illicit Ecstasy tablets, Baggott and colleagues [153] found that 6.5% contained MDA. Similarly, MDA was found in 0.6% of pills submitted to Forensic Science South Australia (FSSA) for testing by South Australia Police (SAPOL) over a 6-month period [154]. It is unclear if these differences are regional, due to differences in illicit drug preparations, or merely differences in sampling. No matter what the actual proportion of Ecstasy pills containing MDA, when we consider the millions of doses of Ecstasy consumed every weekend, there is a strong rationale for studying this drug on its own.

Clinical studies with MDA have been infrequent. MDA was studied in 1941 as a possible therapy for Parkinson's disease [155]. From 1949 to 1957, more than 500 human subjects were given MDA in an investigation of its potential use as an antidepressant and/or anorectic by Smith, Kline, and French. A preliminary report describes administration of doses up to 300 mg/day for periods up to 5 weeks in over 400 people with conditions ranging from mood and anxiety disorders, arthritis-related pain, and psychosis [156]. The United States Army also experimented with the drug, code named EA-1298, while working to develop a truth drug or incapacitating agent. MDA was patented as a cough suppressant by H. D. Brown in 1958, as an "ataractic" (anxiolytic) by Smith, Kline, and French in 1960, and as an anorectic under the trade name "Amphedoxamine" in 1961 [155]. Claudio Naranjo [157] and Richard Yensen et al. [147] each explored MDA as an adjunct to psychotherapy, while Turek et al. [146] administered R-(-)-MDA and Shulgin and

colleagues administered racemic and individual enantiomers [150, 158, 159] for experimental purposes.

Preclinical studies of the pharmacology of MDA in animals have focused on physiological changes [158, 160, 161] and drug discrimination [162, 163]. Overall, MDA appears to be similar to MDMA, with drug discrimination studies suggesting MDA has both hallucinogenic (LSD-like) and MDMA-like properties. Consistent with these *in vivo* results, studies using rat cortex tissue show the R-(-)-enantiomer of MDA has considerable affinity for the 5-HT_{2A}R [164]. However, like MDMA, MDA is not entirely selective for the serotonergic system. MDA can also increase efflux and block reuptake of norepinephrine [161, 165], which may contribute to the drug's effects. **Table 0.1** compares data on the ability of MDA and MDMA to release monoamine neurotransmitters.

Pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy').

MDMA is the N-methyl analogue of MDA. Although pharmacologically complex, as a first level approximation, it may be reasonable in the context of this dissertation to classify MDMA as a 5-HT releaser.

5-HT release appears to be particularly important for MDMA effects [166, 167]. MDMA induces 5-HT release by entering the neuron through the SERT and subsequently causing neurotransmitter storage vesicles to release their contents [168]. Blocking the SERT with an SSRI blocks the ability of MDMA to release 5-HT and decreases many of its effects in animals and humans. For example, Fantegrossi et al. [169] found that self-administration of MDMA in primates was blocked by pre-treatment with a SSRI, a phenomenon that does not occur for stimulants such as cocaine or methamphetamine. In contrast to these stimulants, MDMA-induced dopamine appears to be largely secondary to the release of 5-HT and the subsequent activation of 5-HT_{2A}R [170]. Liechti et al. [171, 172] administered 40 mg intravenous citalopram before 1.5 mg/kg oral MDMA in 16 healthy volunteers (13 were MDMA-naïve), finding that citalopram dramatically inhibited most of the self-report effects of MDMA. Tancer et al. [173] found 20 mg/day oral fluoxetine attenuated the effects of 1.5 mg/kg oral MDMA on self-report rating in ten MDMA-experienced participants. Farré et al. [174] found 20 mg/day oral paroxetine attenuated the effects of 100 mg oral MDMA in twelve MDMA-experienced volunteers. However, as detailed in the previous section and **Table 0.1**, MDMA also interacts with the norepinephrine transporter, and the contributions of noradrenergic changes to MDMA effects are a matter of active research but likely include non-psychoactive physiological changes such as heart rate and blood pressure increases.

MDMA was first synthesized in 1912 by Merck chemist Köllisch as an intermediate compound in the synthesis of methylhydrastinine [175]. However, MDMA received little attention in the next sixty years [176] and apparently did not appear as a street drug in the U.S. until the early 1970s, after MDA had been made a controlled substance. Increasing nonmedical use of MDMA led to its classification as a controlled substance in the 1980s. This classification was controversial because of evidence that MDMA was fundamentally different from most hallucinogens [151] and might be useful in psychotherapy, enabling consideration of stressful issues with reduced fear [177]. Indeed, several psychotherapists

used MDMA in their practices until it was made illegal [177-180], and trials are currently underway or have recently been completed to assess the value of MDMA as an adjunct to psychotherapy in individuals with posttraumatic stress disorder. Recent controlled clinical studies in healthy volunteers appear to confirm that MDMA increases feelings of sociability and closeness to others [17, 181].

In contrast to its robust self-report effects, controlled studies administering MDMA to humans have generally not found impairments or other changes to attention using tasks such as a word-color Stroop [182], continuous performance [183], or digit symbol substitution [184]. In fact, Lamers et al. [185] found that 75 mg oral MDMA improved psychomotor performance, such as movement speed and tracking performance in single task and divided attention tasks. These findings appear to be in contrast to typical effects of 5-HT_{2A}R agonist hallucinogens, which typically slow responding and impair some aspects of attention [186-189]. Although some studies have suggested that evaluation of social and emotional stimuli may be altered by MDMA [17, 18], no studies to date have evaluated potential attentional effects of MDMA using social or emotional stimuli, which I attempt in Chapter 3.

MDMA has unknown bioavailability but is rapidly absorbed following oral administration and attains maximum concentrations in 1-2 hrs [190]. It has an elimination half life of about 6–8 hrs. Main psychoactive effects last for approximately 2-4 hrs with a relatively brief (1-2 hrs) plateau of consistent effects [181, 191], which limits the number of procedures that can be conducted during an experimental MDMA session.

Pharmacology of citalopram. Citalopram is a high-affinity furancarbonitrile selective serotonin reuptake inhibitor (SSRI) that is widely used clinically as an antidepressant. It has high bioavailability and a long (~35 hour) half-life. The main pharmacological effect of citalopram and other SSRIs is the inhibition of the serotonin transporter, which alters the spatiotemporal dynamics of serotonin signaling so that activity in the serotonergic neuron causes greater and more prolonged increases in extracellular serotonin than normal [192-194].

One complex point is that administration of an SSRI to animals has sometimes been found to produce surprisingly small increases in extracellular 5-HT levels in the frontal cortex compared to other brain areas such as the hippocampus or raphe nucleus [192, 195]. This appears to be due to negative feedback controlled by serotonergic somatodendritic and nerve terminal autoreceptors of the neurons.[196-198]. Single administration of an SSRI such as citalopram has been shown to dose-dependently inhibit the firing activity of 5-HT neurons [199, 200]. This has been commonly given as an explanation for why SSRI antidepressants do not immediately produce clinical effects: instead of increasing 5-HT, SSRIs initially decrease it by silencing serotonergic firing. According to this theory, repeated SSRI administration is needed to gradually desensitize 5-HT_{1A}R receptors and allow 5-HT neurons to resume firing.

Because these phenomena are dose-dependent, the crucial question is whether a single dose of 20 mg citalopram facilitates or inhibits serotonergic signaling in humans. Facilitation would be predicted to occur if the duration and absolute extracellular levels

of 5-HT were increased. Inhibition would occur if this increased 5-HT in turn excessively decreased serotonergic firing. 20 mg citalopram is a standard clinical dose and has been used in several cognitive neuroscience experiments. Klein et al. [201] used SPECT and [123 I]ADAM and estimated that $70\pm6\%$ of serotonin transporters are occupied after a single oral dose of 20 mg citalopram, which produced 45.8 ± 7.7 nmol/L citalopram plasma concentration. How does this compare to doses that excessively inhibit serotonergic cell firing in animals? It is difficult to equate doses between species because drug pharmacokinetics depends on many physiological factors that differ between species. Nonetheless, these plasma concentrations appear significantly lower than those that are commonly produced in rodent research. For example, Kugelberg [202] reported peak serum concentrations of approximately 1000 nmol/L after 10 mg/kg subcutaneous citalopram. Accordingly, 10 mg/kg in rats is likely the equivalent of a dose in people that is significantly higher than 20 mg. Yet 10 mg/kg in rats increases rather than decreases extracellular 5-HT in the frontal cortex, with concentrations approximately doubling after 10 mg/kg IP citalopram in rats [203]. Thus, it appears likely that a single dose of citalopram in humans is likely to facilitate rather than inhibit phasic serotonergic release.

Predictions from pharmacological background

In sum, as a 5-HT_{2A}R agonist, MDA should induce pseudo-hallucinations and visual changes. Both MDA and MDMA, as 5-HT releasers, should decrease the attentional salience of threat-related (but not positively-valenced) stimuli, while citalopram, as a SSRI, should increase or leave unchanged the attentional effects of threat-related stimuli. These predictions are tested in the subsequent chapters.

As stated above, I begin by studying hallucinatory syndromes in drug users in Chapter 1 and find them to be common, though the reported unusual visual experiences are not exclusively linked to serotonergic drugs. In Chapters 2 and 3, I use three pharmacological agents to alter serotonergic functioning: 3,4-methylenedioxymphetamine (MDA); 3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’); and the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram. Chapter 2 focuses on mechanisms of hallucinations, while Chapter 3 is dedicated to the effects of the aforementioned drugs on attention to threat-related stimuli.

Table 0.1: Profile of MDA and MDMA as monoamine transporter substrates

Drug	5-HT release EC₅₀ (nM±SD)	NE release EC₅₀ (nM±SD)	DA release EC₅₀ (nM±SD)
RS(±)-MDA	159±12	108±12	290±10
S(+)-MDA	99.6±7.4	98.5±6.1	50.0±8.0
R(-)-MDA	313±21	287±23	900±49
RS(±)-MDMA	74.3±5.6	136±17	278±12
S(+)-MDMA	70.8±5.2	110±16	142±6
R(-)-MDMA	337±34	564±60	3,682±178

Table from [204], collected in rat brain synaptosomes. Substrate activity at SERT, NET, and DAT is reflected as release efficacy for the corresponding transmitter.

CHAPTER 1: Visual Changes in Hallucinogen Users

Despite long-standing reports of prolonged or reoccurring perceptual changes in a subset of hallucinogen users, very little is known about Hallucinogen Persisting Perception Disorder (HPPD) and related visual abnormalities in hallucinogen users. I used an online questionnaire to document the prevalence, symptoms, and relationship to drug use of persisting unusual visual phenomena in hallucinogen users. 16,192 individuals viewed the information sheet, and 2,679 were included in the study. Most participants (61.7%) reported having experienced drug-free visual experiences that resembled hallucinogen effects. Probability of experiencing constant or near-constant symptoms was predicted by greater past exposure to specific hallucinogens, including lysergic acid diethylamide (LSD). Although symptoms were common, few (104, or 3.9 % of the sample) found them distressing or impairing enough to consider seeking treatment.

BACKGROUND

Hallucinogen use is widespread. In the United States, 16.9% of young adults report having used hallucinogens [205]. Although most hallucinogen use apparently occurs without adverse events, there have long been reports of prolonged or reoccurring perceptual changes in a subset of hallucinogen users [206-208]. The 4th edition of the Diagnostic and Statistical Manual of Mental Disorders recognizes this syndrome as Hallucinogen Persisting Perception Disorder (HPPD). Despite many case reports [209-218], very few studies have examined HPPD in a large group of users. I sought to use an online questionnaire as a first step towards documenting the symptoms, prevalence, and relationship to drug use of persisting visual abnormalities in hallucinogen users.

HPPD has been associated with a broader range of drugs than only hallucinogens, which primarily produce effects resembling those of lysergic acid diethylamide (LSD) through serotonergic 5-HT_{2A} receptors [91]. For example, cannabis [218, 219] and 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') [220-222] have been associated with HPPD-like syndromes. The DSM-IV states that HPPD includes any perceptual symptoms reminiscent of acute hallucinogen effects. However, case reports rarely describe any hallucinogen-like effects except visual disturbances. These commonly involve geometric imagery, motion-perception deficits, halos, afterimages, and flashes of color [210-218, 220-223]. To meet DSM-IV criteria for HPPD, symptoms must cause clinically significant impairment or distress, and must not be explainable by other medical conditions. Symptoms may be intermittent or constant and have been reported in some individuals to occur on a daily basis for years (e.g., 9.7 ± 7.7 years in Abraham and Duffy's [224] sample). The duration of symptoms is one distinction between HPPD and the common conception of a 'flashback,' which is usually described as an infrequent, intermittent phenomenon. Although persisting in popular culture, the concept of 'flashback' is no longer considered a useful diagnostic entity [225].

Prevalence of HPPD is considered low [225]. Most studies providing estimates of visual changes in hallucinogen users predate DSM-IV and the HPPD diagnosis, complicating interpretation. Robbins et al reviewed 34 LSD-related psychiatric admissions and found 11 (32%) with “spontaneous return of perceptual distortions or feelings of depersonalization similar to those experienced under the influence of LSD” [226]. However, they also note that at least 8 patients in the case series had a history of psychosis predating LSD use, and they do not specify to what extent these subgroups overlapped. A 10-year follow-up study of 247 individuals who received LSD as part of research (N = 123) or psychotherapy (N = 124) identified five (2%) who described “major perceptual changes” [227]. This included “recurring undulation of visual field” in an unspecified number, suggesting possible HPPD; however, auditory hallucinations were also described in an unspecified number, suggesting possible psychosis. Cohen [228] collected information about ‘hallucinogen-related complications’ from 44 investigators who had studied the effects of LSD or mescaline in a total of 5000 individuals (including both patients and healthy volunteers). While symptoms of HPPD were not explicitly included in the questionnaire, investigators were asked to describe major complications. ‘Fleeting afterimages’ were reported in four subjects who had received mescaline, while no cases were reported for LSD. However, 22 investigators did not respond to the questionnaire, and some adverse events may not have been reported [229]. Together, these studies suggest HPPD is very rare, and raise the question of whether some apparent cases may represent misdiagnosis of other disorders, such as psychosis, epilepsy, migraine aura without headache, or stroke [230-232].

On the other hand, a limited number of publications suggest that chronic visual changes may be relatively common in hallucinogen users. Abraham and colleagues have reported evidence of visual changes not only in HPPD patients, but also in HPPD-free hallucinogen users [233]; published studies include changes in EEG coherence, color perception, and flicker fusion frequency [223, 224, 233-235]. In an unusual animal report, two of four squirrel monkeys developed deficits in size discrimination after prolonged exposure to a high-dose regimen of LSD (10-40 µg/kg daily for four to six months) [236]. These accounts suggest that HPPD may be a severe form of a relatively common syndrome of drug-induced visual changes.

There are no recognized risk factors for HPPD [225]. Although some have reported a relationship between risk of visual changes (or flashbacks) and number of drug exposures [223, 227], others have not [237-239], possibly due to small sample sizes.

Because web questionnaires can be effective in recruiting relatively large samples of difficult-to-reach populations, I conducted a study to identify prevalence and characteristics of self-report visual experiences in hallucinogen users and to find relationships with drug use. Given the paucity of information on HPPD, a web questionnaire seemed appropriate for a first attempt to delineate the types of visual phenomena that this population experiences, despite the obvious limitations of anonymous self-report questionnaires.

METHODS

Participants were recruited from the drug information website erowid.org, which receives approximately 60,000 unique visitors per day. For 80 days, a link on the site invited individuals to complete a "visual experiences survey." Subjects who clicked on the link were shown a study information sheet that did not indicate that chronic visual changes were a focus of the research. Those interested in participating clicked on a link at the bottom of the information sheet and began the questionnaire. Participant anonymity was maintained by using an encrypted hypertext communication protocol and storing encrypted computer network (IP) addresses.

Questionnaire

The survey first obtained participant self-reports of drug-use history as well as past and present psychiatric and neurological diagnoses. It then requested detailed information about participants' visual experiences.

Drug-use history. Questions explicitly asked participants for their number of exposures to 14 specific psychoactives from six pharmacological classes:

1. *classical serotonergic hallucinogens*, including LSD; psilocybin-containing mushrooms; dimethyltryptamine (DMT); 2,5-dimethoxy-4-ethylphenethylamine (2C-E); 2,5-dimethoxy-4-iodophenethylamine (2C-I); 5-methoxy-alpha-methyltryptamine (5-MEO-AMT); alpha-methyltryptamine (AMT); dipropyltryptamine (DPT); and lysergic acid amide (LSA; found in Hawaiian Baby Woodrose seeds)
2. *NMDA antagonists*, including ketamine and high-dose (defined as over 150 mg) dextromethorphan (DXM)
3. MDMA
4. the anticholinergic-containing plant *Datura*
5. cannabis
6. the kappa opioid agonist-containing plant *Salvia divinorum* (*Salvia*)

I selected these drugs based on both anecdotal reports of lasting visual changes and whether I had evidence that the population being recruited was likely to have interest in, and thus possible exposure to, the drugs in question.

In addition, to help ensure the validity of responses, I asked participants about their experience with a fictional drug called "kaopectamine." Those who reported using this drug were excluded from further analysis.

Psychiatric and neurological history. Participants were explicitly asked about past diagnoses (epilepsy or other seizure disorders, migraine, schizophrenia or other psychotic disorders, visual impairments) that are sometimes associated with visual abnormalities. Additional free-response questions allowed descriptions of other diagnosed psychiatric, neurological, or visual difficulties. Four Likert-Scale questions [240], seeking to identify

those with psychotic ideation, asked whether respondents had ever (1) been convinced that other people were watching, talking about, or spying on them; (2) thought they were in danger because someone was plotting to hurt them; (3) thought they had special powers other people did not have; or (4) thought some outside force or power was controlling their body or mind. If there was a positive response to any of these questions, the answers from that participant were removed from the main analyses.

Visual experiences. Respondents were asked about unusual visual experiences with the following question: “Not counting times when (1) you were inebriated or under the influence of any strong psychoactive; or (2) you had taken any of these substances within the last 3 days; or (3) you were in a trance, falling asleep, waking up, or had not slept in a long time, have you had a period in your life when you experienced any of the following visual effects / disturbances?” This question was repeated at the top of each new screen to reduce risk that participants would forget these constraints and answer for other circumstances. The listed visual changes were: “Halos or auras around things” (HALOS); “Stationary things appear to move, breathe, grow, or shrink” (MOVEMENT); “Things that are moving appear to be not moving” (STILL); “Things that are moving leave afterimages behind” (TRAILS); “Colors increase in brightness or intensity” (COLORS); “You see with open eyes patterns or textures that are not really there” (PATTERNS); “You see with open eyes things or objects that are not really there” (THINGS); “Oscillations or flashing light sources, as in TVs or fluorescent lights, bother you more than other times in your life” (OSCILL); “Grids, gratings or closely spaced lines bother you more than other times in your life” (GRIDS).

Respondents who endorsed any of the first seven listed visual experiences were asked further Likert-Scale questions about the frequency and phenomenology of these experiences. They were also asked for a free-text description of a specific time when the most vivid one had occurred. In addition, these respondents were asked whether these visual experiences overall had been so troublesome, or had made social, work, school, or other activities so difficult, that they considered getting professional treatment.

Participants reporting drug-free visual phenomena were asked if they thought a specific event triggered these symptoms or made them significantly worse. Those affirming a trigger event were asked to describe the event, their age at the time, any drugs used in the week before the event, whether the symptoms occurring after the event had also occurred prior, and whether, in the week before the trigger event, they had experienced head injury, loss of consciousness, sickness or inflammation, decreased visual ability, or had begun or changed the dose of a prescription drug.

Inclusion / Exclusion Criteria

Responses were excluded from analysis if (1) they were unfinished; (2) multiple submissions came rapidly (less than 10 minutes apart) from a single IP address; (3) respondents reported they were not fluent in English or had difficulty understanding the questions; (4) respondents reported use of the fictional drug “kaopectamine”; (5) respondents reported no past hallucinogen use; or (6) free-response or catch answers

suggested submission was not serious or that the respondent was describing acute drug effects. Respondents who appeared to consistently describe acute drug effects when asked to provide an example of a visual symptom were excluded.

Data analysis

Because estimated numbers of exposures to each drug were not normally distributed, numbers were log10 transformed for analysis. Medians were reported when continuous variables were skewed. Categorical variables were analyzed using Fisher's Exact Test with odds ratios (OR) and 95% confidence intervals (CI) calculated. Analyses focused on three main measures: number of unusual visual experiences endorsed (NUMSYMPT); number of constantly (or nearly constantly) occurring visual symptoms reported (NUMCONSTANT); and whether the participant found the symptoms so distressing or debilitating that treatment was considered or sought to diminish their symptoms (SEEKTREAT). NUMSYMPT was selected to liberally include even brief or single unusual experiences, while NUMCONSTANT attempted to identify individuals with truly abnormal visual experiences. SEEKTREAT was used to provide an indication of what, if any, symptoms might be clinically significant. To determine variables independently associated with these measures, multiple logistic regressions were conducted using Poisson models to predict number of symptoms or binomial models to predict presence of symptoms. Backwards elimination of variables was used, meaning that all candidate variables were initially included in models and those that were not significantly predictive of outcome were removed from the final model. Chi-squared tests were used to identify significant models. All analyses were conducted using R [241].

RESULTS

Respondents. 3,139 responses were collected over an 80-day period, representing 19.4% of the 16,192 who viewed the information sheet. 2,679, or 85.3%, of these responses met inclusion criteria. Reasons for exclusion were as follows: unfinished responses (283, or 9%); duplicate responses (126, or 4%, in all cases an artifact that resulted from participants hitting the submit button twice); reported difficulty understanding the questionnaire (31, or 1%); appeared to be describing acute drug effects (17, or 0.5%), and reported no history of hallucinogen use (three, or 0.1%). No participants of the 2,679 were excluded for apparently unserious submissions.

Respondents were 89.5% male, aged 21.6 ± 3.7 years (range: 13–77). Most lived in the United States (68.9%), with lower numbers residing in Canada (9.0%), the United Kingdom (5.8%), Australia (3.6%), the Netherlands (1.4%), Sweden (1.1%), and other countries (10.2%).

Drug use and prevalence of visual experiences. Respondents had extensive drug histories (**Table 1.1**), reporting a median of 5 different drugs used (out of 15 listed). 1,652 (61.7%) of all 2,679 respondents reported at least one of the nine visual experiences reminiscent of hallucinogen effects.

Occurrence of psychiatric and neurological diagnoses. Because some respondents reported diagnoses that would complicate interpretation of their visual experiences, I initially compared those individuals to the remaining sample before focusing analyses on those without complicating diagnoses. 224 respondents (8.4%) of 2,679 reported having one of six diagnoses associated with unusual visual experiences: migraine (110, or 4.1%), history of eye disease (51, or 1.9%), psychosis (38, or 1.4%), PTSD (33, or 1.2%), epilepsy (13, or 0.49%), and stroke (3, or 0.11%). Prevalence of visual experiences was compared between members of each of these groups and all other participants using Fisher's exact test. Respondents with either PTSD (OR 6.31, 95%CI: 1.95-32.4, $p < 0.001$) or psychotic disorders (OR 4.16, 95%CI: 1.61-13.7, $p = 0.001$) were more likely to have at least one type of unusual visual experience compared to all those without each disorder. In order to better characterize putatively drug-related visual experiences, these 224 individuals were excluded from further analyses.

In the remaining 2,455 individuals, I measured reported histories of three additional diagnoses: anxiety disorders (147, or 6.0%), depression (331, or 13.5%), and obsessive-compulsive disorder (51, or 2.1 %). Visual changes are not typically associated with these disorders. Nonetheless, visual experiences were more likely in individuals with either past anxiety disorders (OR 2.01, 95%CI: 1.36-3.03, $p = 0.001$) or depression (OR 1.50, 95%CI: 1.16-1.94, $p < 0.001$).

Visual experiences reported in drug users without complicating diagnoses. 1,487 (60.6%) of the remaining individuals reported at least one of the nine visual experiences that were included in the questionnaire. 587 (23.9%) endorsed at least one experience on a constant or near-constant basis (**Table 1.2**). In a free-text response, 278 (11.3%) reported at least one experience in addition to the nine experiences included in the questionnaire, the most common of which are summarized in **Table 1.3**.

Relationship between visual experiences and drug use. In order to test for relationships between self-reported visual experiences and drug use, I began by assessing number of types of reported visual experiences (NUMSYMPT). A Poisson regression model predicting NUMSYMPT from log₁₀-transformed exposures to individual drugs was statistically significant (chi-squared = 392.38, df = 8, $p < 0.001$). Log₁₀ exposures to LSD, LSA, mushrooms, DXM, ketamine, 2C-E, DPT, and Salvia were significant predictors of NUMSYMPT. Estimates were similar for most hallucinogens, and ranged from 0.795 for DPT to 1.23 for LSD. In other words, for example, each log₁₀-unit increase in LSD exposures led to an expected increase of 1.23 additional types of experiences.

I hypothesized that reporting constant or nearly constant changes might be a more reliable indication of truly abnormal visual changes than simply having ever had a given

experience. Therefore, I made a Poisson regression that predicted the number of constantly or near-constantly occurring experiences (NUMCONSTANT) from \log_{10} -transformed exposures to individual drugs (chi-squared 394.34, $df = 5$, $p < 0.001$). \log_{10} -transformed exposures to 2C-E, LSD, DXM, LSA, and AMT were significant predictors of NUMCONSTANT. Each \log_{10} -unit increase in drug exposure was predicted to increase the number of constant experiences by 1.79 for 2C-E, 1.53 for LSD, 1.51 for DXM, 1.33 for LSA, and 0.67 for AMT. Similarly, binomial models were constructed to predict the presence or absence of any experience, as well as individual experiences with different drugs. Significant predictor drugs and estimated odds ratios are summarized in **Table 1.4**. **Figures 1.1-1.8** illustrate the probability of having at least one constant symptom as predicted by exposures to different drugs.

Treatment-seeking participants. 104 of 2,455 (4.2%) said their visual experiences were initially or currently sufficiently troublesome to have prompted thoughts of treatment. Of the 104 participants who considered seeking treatment at any point, only 27 (26%) had actually sought treatment. Ninety of the 104 individuals had considered seeking treatment during the first 2 months of symptom onset, while only 20 of these 90 (22%) currently would.

Constant symptoms increased likelihood of a participant considering or actually seeking treatment from a healthcare provider (OR 9.76, 95%CI: 6.18-15.82, $p < 0.001$); however, only 12.9% of those who reported any constant symptoms considered treatment. Thus, these perceptual experiences, even when constant, were not necessarily problematic. In describing their experiences, many participants commented that, for example, it was “[n]ot really a negative thing; kind of neutral. It’s become normal. Actually, the low-light patterning hallucinations are quite beautiful and enjoyable.” Similarly, another participant wrote that “visuals of drugs are present when I am not tripping now because I notice how things change more or how light is formed of different ways. It makes me feel like a kid again because I enjoy the simple things in life, like light patterns.”

Variables predicting treatment seeking. What individual experiences and/or particular drugs were more likely to predict thoughts of seeking treatment? In a logistic regression, where constantly or nearly constantly experiencing the nine main individual experiences were used to predict thoughts of treatment seeking (SEEKTREAT), only HALOS, MOVEMENT, PATTERNS, and THINGS were significant (see **Table 1.5**). Of the experiences that were volunteered in the free response, static vision (OR 8.41, 95%CI: 2.32-25.3, $p < 0.001$), difficulty focusing (OR 7.85, 95%CI: 2.19-23.3, $p = 0.001$), alterations in color perception (OR 4.95, 95%CI: 0.898-18.1, $p = 0.0326$), and illusory perceptions of flickering (OR 4.93, 95%CI: 1.94-11.1, $p < 0.001$) were associated with SEEKTREAT using Fisher’s exact tests. In a test of whether SEEKTREAT was associated with specific drugs, a binomial model was significant, with SEEKTREAT being significantly predicted only by \log_{10} exposures to 2C-E (OR 2.29, 95%CI 0.98-4.60, $p = 0.03$) and DXM (OR 1.43, 95%CI 1.04-1.92, $p = 0.02$).

Endorsement of a precipitating episode that began visual changes. 13.9% (262 of 1,487) of participants who reported visual experiences and lacked complicating diagnoses

felt that their experiences were triggered by a specific episode (that is, their experiences had a sudden onset). Most of these individuals (191 of 262, or 72.1%) reported they had never experienced these visual change(s) on any previous occasion. Of those reporting triggering episodes, 45 (17.2%) considered or actually sought treatment. Six of these 45 (13.3%) reported non-drug events in the week before onset, such as illness or loss of consciousness. When asked to recall anything unusual about the triggering episode, free-text responses by participants mentioned an unusually high dose or strong effects (45 out of 262, or 17.2%), an acute dysphoric response to the drug (26 out of 262, or 9.9%), or first exposure to the specific drug (22 out of 262, or 8.4%). Thus, visual experiences appear not to be uniquely associated with any of these factors. Drugs reported to have been used in the week before the experiences are summarized in **Table 1.6**.

Treatment-seeking participants with a precipitating episode that began with visual changes. In order to analyze the subset of participants who were most likely to be diagnosed with an HPPD-like syndrome, I next considered those 45 individuals who reported a sudden onset of symptoms after drug exposure and considered seeking treatment. This was done because I wanted to determine whether the temporal relationship between symptom onset and drug use increased likelihood that drug exposure actually contributed to the symptoms. It is possible that apparent cases of HPPD may sometimes represent misdiagnosis of other syndromes, including psychosis. I therefore compared age, drug exposures, paranoid ideation, and visual experiences between the 45 HPPD-like participants and the 30 individuals in my sample who reported events related to psychosis (and no other complicating diagnosis).

While age and drug exposures were not significantly different between the two subgroups, there were differences in paranoid ideation and visual experiences. Those with a past diagnosis of psychosis were significantly more likely to endorse three of four questions designed to measure psychotic ideation: having felt they were being spied on (79% vs. 44%, OR 4.97, 95%CI 1.66 - 16.56, $p = 0.002$), possessed special powers (64% vs. 27%, OR 4.70, 95%CI 1.65 - 14.24, $p = 0.001$), or being influenced by an outside force (54% vs. 22%, OR 4.12 4.70, 95%CI 1.42 - 12.65 $p = 0.004$). A fourth question, feeling in danger due to plots by others, did not achieve significance, but the effects were in the same direction ($p = 0.088$). Regarding visual experiences, those with psychosis were significantly less likely to report MOVEMENT (42% vs. 73%, OR 0.27 95%CI 0.092 - 0.77, $p = 0.0096$). A trend for those with psychosis to be less likely to endorse PATTERNS did not achieve significance but tended in that direction ($p = 0.066$). When constant or nearly constant experiences were examined, those with psychosis were found to be less likely to experience constant HALOS (18% vs. 44%, OR 0.28, 95%CI 0.0794 - 0.881, $p = 0.017$) or PATTERNS (18% vs. 40%, OR 0.338, 95%CI 0.0946 - 1.06, $p = 0.049$).

Phenomenology of HPPD-like experiences. Descriptions written by the 45 individuals with HPPD-like experiences were diverse, making summary difficult. Their reports rarely included hallucinatory or illusory perception of THINGS or objects, except when forms were incorporated into illusory patterns or when participants experienced brief peripheral percepts. (e.g., “This is only in my peripheral vision. I see things run past me;

and I turn to look and there is nothing there. It used to scare me.”) The PATTERNS described either appeared in front of the visual scene as if floating in space, or were incorporated into the surfaces of things like walls and carpets. Most (64.2%) said PATTERNS appeared flat and two-dimensional. PATTERNS had no obvious preponderance for particular shapes; while some participants perceived circular forms, others saw angular or fractal patterns. A few described seeing more elaborate forms, such as eyes, embedded in patterns. Both PATTERNS and MOVEMENT were described as often being triggered by looking at textured surfaces, such as walls and carpets. Multiple symptoms were often experienced simultaneously. For example, one person wrote, “staring at my carpet floor I saw it wave and move as water in slow motion. Eyes begin to appear along with faces and it all melts and waves together.” In addition to illusory movement of motionless objects, participants described impairments in perceiving actual motion. The phenomenology of these motion perception deficits was not uniformly described. TRAILS or afterimages behind subjectively or objectively moving objects sometimes appeared as persisting negative afterimages. (“Whenever I look at a stationary object and turn my head; I can still see the object; only its color is turned into a very dark shade of a rainbow.”) Other times they were described as blurry trails or a series of strobe-like percepts (“the object moved with white-colored frame type images trailing from it”) behind the object.

DISCUSSION

I used a web-based questionnaire to collect self-report data on unusual drug-free visual experiences in hallucinogen users and found that their reports of such experiences were strikingly common. I collected 3,139 responses and excluded 460 responses that were incomplete, duplicated, reflected difficulty understanding the questionnaire, or were from individuals without reported hallucinogen use. 61.7% of the remaining 2,679 respondents reported visual experiences reminiscent of hallucinogen effects occurring when they had not used a drug within three days. However, in the majority of cases, these experiences appeared to not have been clinically significant. Only 104 (3.9%) participants found the visual experiences so distressing or impairing that they considered or actually sought treatment for their symptoms. These 104 represent a small portion of the 2,679 who were included in the study and 0.64% of the 16,192 who viewed the information sheet. If this group is further limited to the 45 who reported a clear temporal relationship between drug use and symptom onset, it can be estimated that HPPD-like abnormal visual symptoms occurred in 1.7% of participants, and at least 0.28% of those considering participation. Thus, while unusual and persisting visual experiences are relatively common in hallucinogen users (or at least more common than expected), symptoms that cause consideration of treatment-seeking appear relatively rare.

There are limited data on recovery from HPPD symptoms (partly because there are limited data on its prevalence to begin with). I was not able to statistically estimate a relationship between time and a decrease in symptom severity. However, many respondents described experiences that resolved within a week or two. Furthermore, only a minority (22 of 104) of those who had initially considered seeking treatment (during the first 2 months after onset) would currently consider their symptoms impairing or

distressing enough to seek treatment. This suggests either decreased symptoms or accommodation to the symptoms. In a rare report to examine recovery, Holstein [242] conducted a follow-up study in polydrug-using patients who were being treated in a psychiatric hospital and who reported ‘flashbacks.’ An initial clinical interview determined that 53 out of 91 participants reported flashbacks; on follow-up, 1.5–4 years later, 35 still reported flashbacks, with symptoms generally less intense than initially. Abstinence from drug use – which I did not measure – appeared to be associated with better outcomes in that report. Thus, my data are consistent with the limited evidence that symptoms may partly or fully resolve in many individuals.

One theory states that HPPD results from abnormal cellular responses induced by the drug in the visual system. Abraham et al, for example, hypothesized that HPPD was due to loss of serotonergic receptors on inhibitory interneurons [243]. However, while NMDA antagonists can produce lesions in rodents [244] and MDMA can cause long-term monoaminergic changes in rodents [170], there are no reports confirming persisting changes in receptors or neurotoxicity in animals or humans after exposure to serotonergic hallucinogens like LSD. Nor is it clear why pharmacologically disparate drugs (such as LSD, DXM, and Salvia) would all produce persisting visual experiences. Together, these findings suggest that some forms of HPPD-like visual phenomena might be due to some individual vulnerability that can be triggered by drug exposure.

If there are consistent alterations in the visual system of people with HPPD-like experiences, it seems more likely that they involve the magnocellular rather than parvocellular visual pathway. The relative lack of form perception deficits and frequency of motion-related complaints, as well as an apparent association of symptoms with low-light and peripheral visual fields, are arguably consistent with decreased magnocellular fidelity. Laboratory testing would be needed to confirm this speculation and to investigate at which level of the visual system these abnormalities might originate. For example, changes could occur in the primary visual cortex, where serotonergic cells are reportedly biased for modulating magnocellular pathways [245]. Alternatively, there might be retinal changes analogous to those produced by the 5-HT₂-antagonist antidepressant nefazadone, which produces HPPD-like symptoms through lasting retinal toxicity that is detectable with multifocal electroretinogram [246].

A second possibility is that some HPPD-like visual experiences in drug users reflect increased awareness of normal visual phenomena that are usually selectively ignored but which become more noticeable after one has similar experiences under the influence of a hallucinogen. In Bayesian terms, the prior likelihood of hallucinogen-like visual experience has been increased by experience. Therefore, when signals are variable or ambiguous, they become more likely to be interpreted as hallucinogen-like. This theory would predict that experiences should decrease with time and abstinence from drug use. This appears consistent with the detected relationships between log₁₀-transformed number of drug exposures and visual experiences.

Relationships were seen between number of drug exposures and both number of experiences (of any frequency) and number of constant or near-constant experiences. Several investigators [237-239] have failed to detect such a relationship, possibly because

of the smaller sample sizes and the larger proportion of participants with clinically significant changes in their samples. My results, in contrast, suggest an increased likelihood of unusual visual experiences as individuals increase their drug exposures.

Several specific drugs were statistically associated with unusual visual experiences in my sample. LSD appeared to be the most robust predictor, consistent with its prominence in case reports of HPPD [225, 247]. Nonetheless, even for this drug, the absolute risk of reporting unusual persistent visual experiences was only modestly increased by LSD exposure. For the 1,016 respondents who reported no LSD use, the prevalence of any constant visual experience was 18.1%, and this number approximately doubled to 34.5% in the 525 individuals who had used LSD 10 or more times. Prevalence of any unusual experience (whether constant or not) was 54.1% in those who reported no LSD use and rose to 69.5% in those who had used LSD 10 or more times.

The increased likelihood of unusual visual experiences associated with these drugs, however, cannot necessarily be equated with increased risk of HPPD. In fact, I detected few relationships between drug exposure and having distressing or impairing symptoms that engendered thoughts of professional treatment. Only two drugs were significantly linked to these thoughts or actions, 2C-E and DXM. Curiously, these drugs have very different pharmacology. 2C-E is a relatively unstudied phenethylamine that appears to be a classical 5-HT_{2A}-agonist hallucinogen [159, 248], while DXM is a widely used cough suppressant that, in high doses, is metabolized to psychoactive amounts of the NMDA-receptor antagonist dextrorphan. No other drugs, despite several with very similar pharmacology, significantly predicted thoughts of seeking treatment.

There are a number of possible explanations for this finding. From a statistical perspective, individuals are likely to stop using drugs at the onset of worrisome symptoms, while others will continue to use them, which will obscure a relationship. In addition, treatment-seeking likely reflects, in part, the individual's degree of anxiety, presence of nonvisual symptoms, and interpretation of the meaning of their symptoms – none of which I systematically assessed. Thus, a statistically significant relationship with considering treatment may be most readily detected in drugs with very low prevalence and number of exposures (2C-E) or drugs with high prevalence that can produce other non-visual but worrisome symptoms, such as cognitive impairments (DXM). Evidence for this possibility comes from the list of drugs that participants said were temporally related to symptom onset. These temporally coincident drugs were most commonly LSD, psilocybin, high-dose DXM, and MDMA. With the exception of DXM, these have been previously associated with HPPD-like changes in case reports [209, 217, 220-222, 249]. Given the extensive drug use in my sample, I cannot discount the possibility that the temporal relationship between drug use and symptom onset may have been coincidental in some cases. Nonetheless, free-text responses that described experiences that first developed during drug intoxication and then lingered for days, weeks, or longer suggest the temporal relationship was not always coincidental.

It has been suggested or implied that apparent cases of HPPD may sometimes represent misdiagnosis of psychosis. Although often associated with auditory hallucinations, prodromal and first-episode psychosis may include visual symptoms [250, 251], possibly

relating to perceptual hypersensitivity and dysfunction in the magnocellular visual pathway [252]. For example, Klosterkötter et al. (2001) reported that the presence of self-reported visual perception anomalies predicted eventual development of first-episode psychosis with a sensitivity of 0.46 and a specificity of 0.85. Furthermore, many of my participants were young adults, in the age range when first episodes of psychosis are most likely to occur [253]. Nonetheless, the differences in visual experiences and paranoid ideation between those who reported signs of psychosis and those with HPPD-like complaints argues against undiagnosed or prodromal psychosis explaining the majority of the HPPD-like experiences in my sample.

The major limitation of this study is that it relied entirely on self-report data. Although the length of the questionnaire and my various data-integrity checks likely minimized unserious responses, key data—such as drug intake, visual experiences, and past diagnoses—may have been inaccurately reported even by those making good-faith attempts to give accurate data. The self-report nature of the study also ensures that I cannot diagnose any participants with HPPD, or any other syndrome for that matter. Distinguishing between HPPD and, for example, persistent migrainous visual aura without headache would likely be difficult even with a detailed examination [231, 232]. Nevertheless, given the limited knowledge of the frequency and persistence of HPPD in drug users, the present findings are a first approximation, and the results invite more research into this phenomenon.

In conclusion, I collected self-report data indicating that seemingly unusual drug-free visual experiences reminiscent of acute drug effects are common in hallucinogen users. Although only a few participants reported clinically distressing or impairing symptoms, many more reported their existence. More extensive use of LSD and several other hallucinogens significantly, if modestly, increased the probability of reporting unusual visual experiences. The results signify that more objective testing of visual functioning in hallucinogen-using populations is warranted and could clarify mechanisms of HPPD and the effects of these drugs on the visual system.

Table 1.1: Reported drug use history in full sample (N = 2679)

Drug	Percent Using	Reported Number of Exposures Among those Using		
		25th percentile	Median	75th percentile
Cannabis	98.7%	100	500	1000
Mushrooms	82.7%	3	6	15
Salvia	61.1%	2	4	7
LSD	58.7%	2	5	20
MDMA	58.0%	3	8	25
DXM	49.5%	2	4	10
LSA	32.4%	1	2	4
Ketamine	22.1%	1	3	10
DMT	15.4%	1	2	6
2C-I	15.2%	1	3	5
2C-E	6.9%	1	2	5
Datura	6.5%	1	1	3
AMT	5.7%	1	2	5
5-MEO-AMT	5.3%	1	2	6
DPT	3.6%	1	3	6

Table 1.2: Symptoms among those without complicating diagnoses (N = 2,455)

	Ever Occurred	Constantly Occurs	Example Description
MOVEMENT	833 (33.9%)	212 (8.6%)	“I had taken a large amount of mushrooms throughout a day. Afterwards for about a week I would get times where objects appeared to be breathing and objects seemed to slowly move.”
COLORS	635 (25.9%)	199 (8.1%)	“Sometimes a color-shift will occur; and certain objects/colors will become very intense – standing out from the background.”
PATTERNS	594 (24.2%)	216 (8.8%)	“Stayed up all night on MDMA and started seeing yellow hexagons on a white wall. I was admiring this the next day too when someone told me the wall was blank. I still see yellow hexagons on any blank surface.”
OSCILL	549 (22.4%)	NA (NA)	NA
TRAIL	543 (22.1%)	227 (9.2%)	“When you wave your hand in front of your face or in your field of vision you will appear to have many hands following your hand.”
HALOS	503 (20.5%)	178 (7.3%)	“This happens often when I am watching people from far away. They appear to have halos over their heads and their body parts also leave impressions as they move.”
GRIDS	444 (18.1%)	NA (NA)	NA
STILL	186 (7.6%)	37 (1.5%)	“Traffic appears like comic book images – cartoon-like; frame by frame with dynamic illustration of velocity.”
THINGS	154 (6.3%)	29 (1.2%)	“The week before I had taken 2 grams of mushrooms; 1 blotter hit of acid; about 10 grams of marijuana; and about 2 grams of DXM powder. The most vivid of the things to happen after the effects had worn off happened in my bedroom one morning about 1 week after. Gigantic transparent spiders were in my bed; standing in my bedroom. They didn't move but stayed in the same place. I left the room and went into my bathroom and everything was normal; but going back into my bedroom they were still there.”

Table 1.3: Other commonly described symptoms (N = 278)

Symptom	Percent (of 278)	Example Description
Awareness of floaters, dots, or unstructured collections of small forms	20.6%	“I was staring at the blue sky; when I noticed what [I] immediately thought of as quarks. They looked like tiny white dots that would move a short distance in a random direction?; leaving a short lived trace as they did. It was like watching life under a microscope.”
Flickering	17.1%	“Immediately after taking a combination of MDMA/Methylone; I noticed occasional strobe like flash of light in the ear side corner of my left eye. I have had it chronically ever since. At first it would return every 6 weeks or so and last for two to three weeks. Recently; it seems to be abating. Symptoms are much less intense and much less frequent. I continue to see 'noise' in the corner of my left eye after moving from a darkly lit area to a brighter lit area; or when I am in front of a bright fluorescent light source. Sometimes this is quite distressing.”
Feeling that the visual scene is sharper, cartoonish, or unreal	11.1%	“It was almost like a flashback to a previous experience while on psychedelics. It seems as though the object is so in focus that I can observe more than most about it.”
Closed-eye visuals	8.4%	“Images of people when eyes closed several days after MDMA use ... patterns when my eyes are shut - same as when I'm tripping.”
Increased difficulty focusing	8.0%	“With open eyes having trouble focusing on [things in] plain view up to a week after the experience [with Ecstasy].”
Static vision	7.3%	“Walls always seem to be made out of little dots; sort of like electronic snow/TV fuzz.”
Alterations in color perception	6.6%	“I took E and Shrooms in the same week- after closing my eyes; I still saw the same patterns I did when I was tripping. I also had tracers; and couldn't tell what color traffic lights were.”

Table 1.4: Results of models predicting constant symptoms

Outcome	Final Model	Predictor	OR	95% CI	p-value
Any Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log LSD	1.63	1.41–1.88	< 0.001
Any Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log DXM	1.59	1.34–1.88	< 0.001
Any Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log 2C-E	2.17	1.30–3.66	0.003
Any Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log DPT	0.415	0.20–0.83	0.016
Any Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log LSA	1.53	1.14–2.06	0.004
HALOS Constant	~ log LSD + log DXM + log AMT + log Datura	log LSD	1.9	1.54–2.33	< 0.001
HALOS Constant	~ log LSD + log DXM + log AMT + log Datura	log DXM	1.78	1.40–2.25	< 0.001
HALOS Constant	~ log LSD + log DXM + log AMT + log Datura	log AMT	0.484	0.18–1.06	0.1
HALOS Constant	~ log LSD + log DXM + log AMT + log Datura	log Datura	1.53	1.05–2.17	0.02
MOVEMENT Constant	~ log LSD + log DXM + log 2C-E	Log LSD	1.26	1.02–1.54	0.028
MOVEMENT Constant	~ log LSD + log DXM + log 2C-E	log DXM	1.67	1.34–2.07	< 0.001
MOVEMENT Constant	~ log LSD + log DXM + log 2C-E	log 2C-E	2.28	1.24–3.99	0.005
STILL Constant	~ log DPT	log DPT	4.96	1.47–12.58	0.002
TRAILS Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log LSD	2.12	1.75–2.56	< 0.001
TRAILS Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log DXM	1.81	1.44–2.27	< 0.001
TRAILS Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log 2C-E	2.61	1.41–4.75	0.002
TRAILS Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log DPT	0.338	0.12–0.81	0.022
TRAILS Constant	~ log LSD + log DXM + log 2C-E + log DPT + log LSA	log LSA	1.67	1.12–2.46	0.011

Table 1.4: Results of models predicting constant symptoms

Outcome	Final Model	Predictor	OR	95% CI	p-value
COLORS Constant	~ log LSD + log DXM + log 2C-E	log LSD	1.53	1.24–1.86	< 0.001
COLORS Constant	~ log LSD + log DXM + log 2C-E	log DXM	1.66	1.32–2.07	< 0.001
COLORS Constant	~ log LSD + log DXM + log 2C-E	log 2C-E	2.19	1.19–3.85	0.009
PATTERNS Constant	~ log LSD + log DXM + log 2C-I + log Datura	log LSD	1.78	1.47–2.16	< 0.001
PATTERNS Constant	~ log LSD + log DXM + log 2C-I + log Datura	log DXM	1.66	1.33–2.06	< 0.001
PATTERNS Constant	~ log LSD + log DXM + log 2C-I + log Datura	log 2C-I	1.92	1.28–2.82	0.001
PATTERNS Constant	~ log LSD + log DXM + log 2C-I + log Datura	log Datura	1.36	0.95–1.91	0.083

Table 1.5: Results of models predicting treatment-seeking

Outcome	Final Model	Predictor	OR	95% CI	p-value
SEEKTREAT	~ HALOS Constant + MOVEMENT Constant + PATTERNS Constant + THINGS Constant	HALOS Constant	3.18	1.86- 5.34	< 0.001
SEEKTREAT	~ HALOS Constant + MOVEMENT Constant + PATTERNS Constant + THINGS Constant	MOVEMENT Constant	3.17	1.87- 5.25	< 0.001
SEEKTREAT	~ HALOS Constant + MOVEMENT Constant + PATTERNS Constant + THINGS Constant	PATTERNS Constant	2.91	1.72- 4.85	< 0.001
SEEKTREAT	~ HALOS Constant + MOVEMENT Constant + PATTERNS Constant + THINGS Constant	THINGS Constant	5.75	2.36- 13.73	< 0.001
SEEKTREAT	~ log DXM + log 2C-E	log DXM	1.43	1.04- 1.92	0.02
SEEKTREAT	~ log DXM + log 2C-E	log 2C-E	2.29	0.98- 4.60	0.03

Table 1.6: Drugs associated with sudden symptom-onset

	Number of triggering episodes	% of triggering episodes
LSD	81	31%
Psilocybin	64	24%
MDMA	41	16%
DXM	35	13%
Salvia	13	5%
2C-I	13	5%
LSA	12	5%
AMT	7	3%
Ketamine	6	2%
DMT	6	2%
2C-E	5	2%
5-MEO-AMT	4	2%
Datura	3	1%
DPT	2	1%

Figures 1.1-8: Probability of having at least one constant symptom predicted by drug exposures

Each group of plots depicts a single multivariate regression of the relationship between constant symptoms and drugs shown to significantly predict them. Upper ticks in each plot represent individuals who experience the constant symptom(s), while lower ticks represent individuals who do not. Solid lines indicate estimates of the proportion of respondents reporting the symptom(s), using naïve locally weighted regression fit for these data. Dotted lines indicate the result of a locally weighted regression using *predicted values*. Thus, comparison between solid and dotted lines illustrates the fit between the actual and predicted values. Dashed lines indicate predictions when all model variables (i.e., drug exposures) except the plotted drug are held to their means. The dashed lines, therefore, emphasize the predicted effects of the plotted drug (in contrast to the dotted lines which include the influence of all significant drugs).

Figure 1.1: ANY CONSTANT SYMPTOM~ log LSD + log DXM + log 2CE + log DPT + log LSA

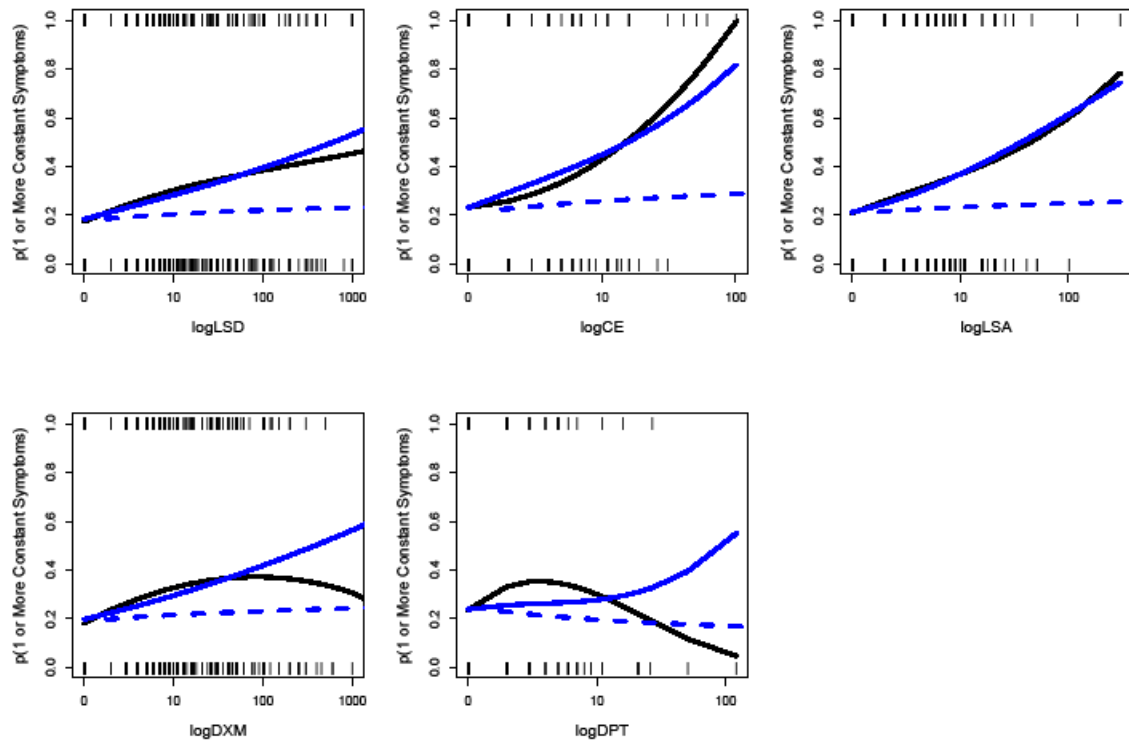


Figure 1.2: Constant Halos $\sim \log \text{LSD} + \log \text{DXM} + \log \text{AMT} + \log \text{Datura}$

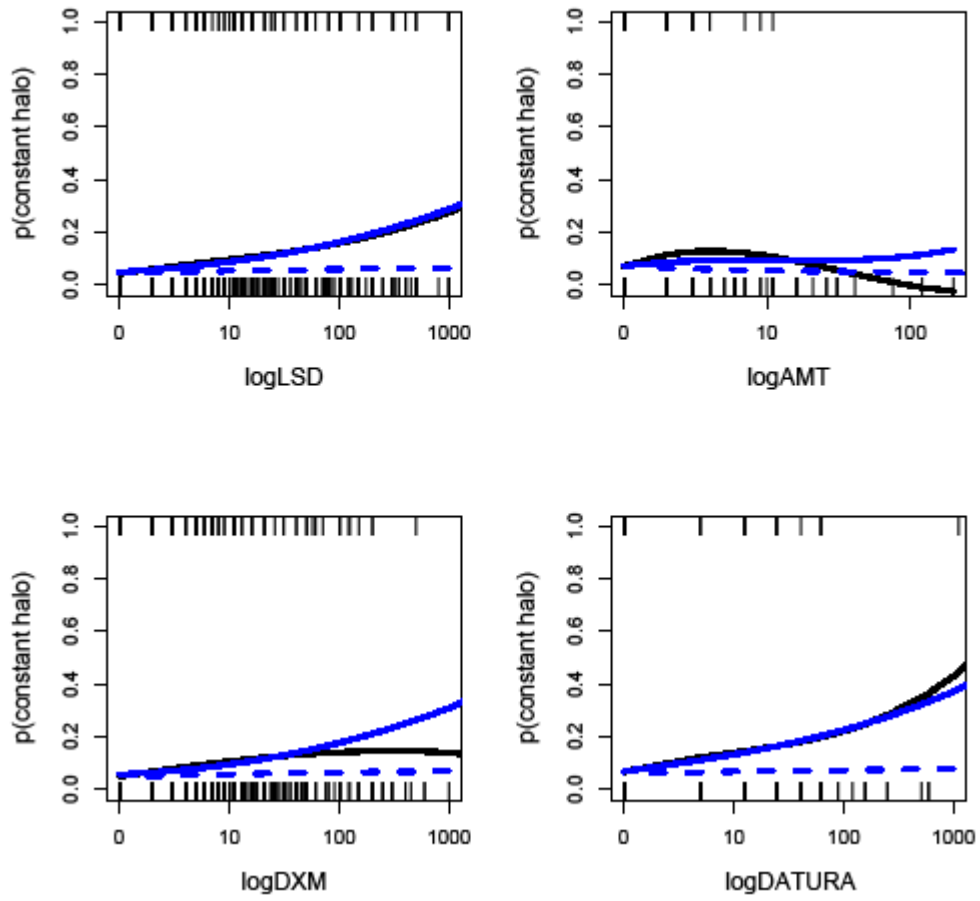


Figure 1.3: Constant Illusory Movement $\sim \log \text{LSD} + \log \text{DXM} + \log \text{CE}$

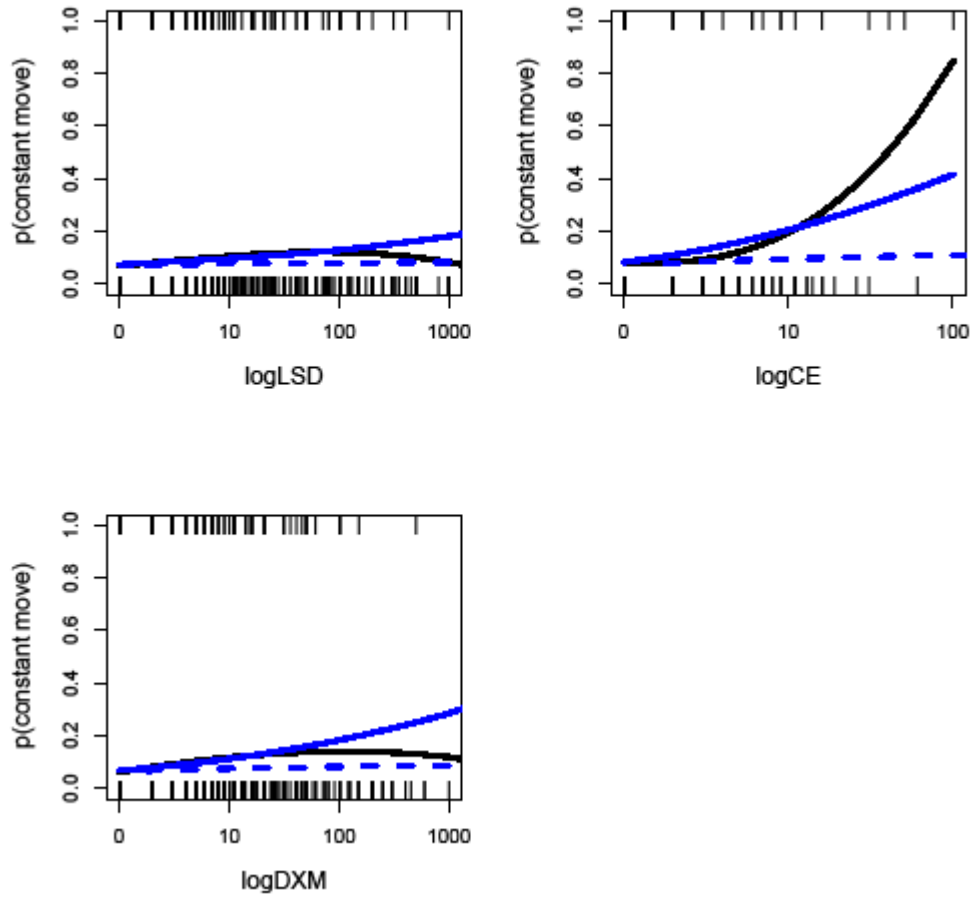


Figure 1.4: THINGS MOVING SEEM STILL $\sim \log$ DPT

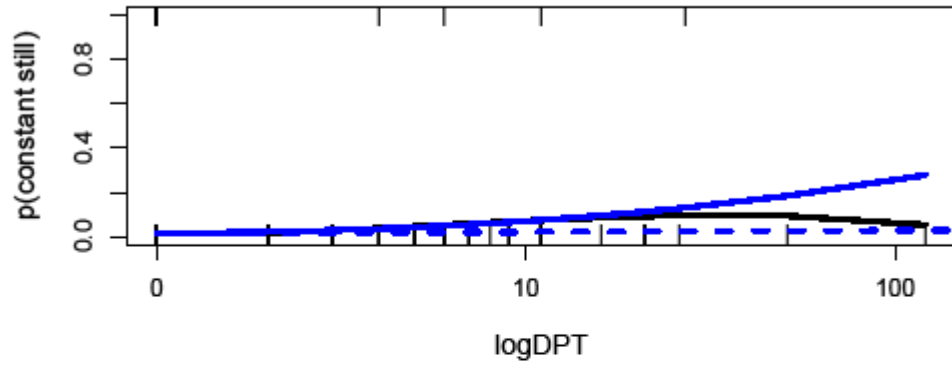


Figure 1.5: CONSTANT TRAILS $\sim \log \text{LSD} + \log \text{DXM} + \log \text{CE} + \log \text{DPT} + \log \text{LSA}$

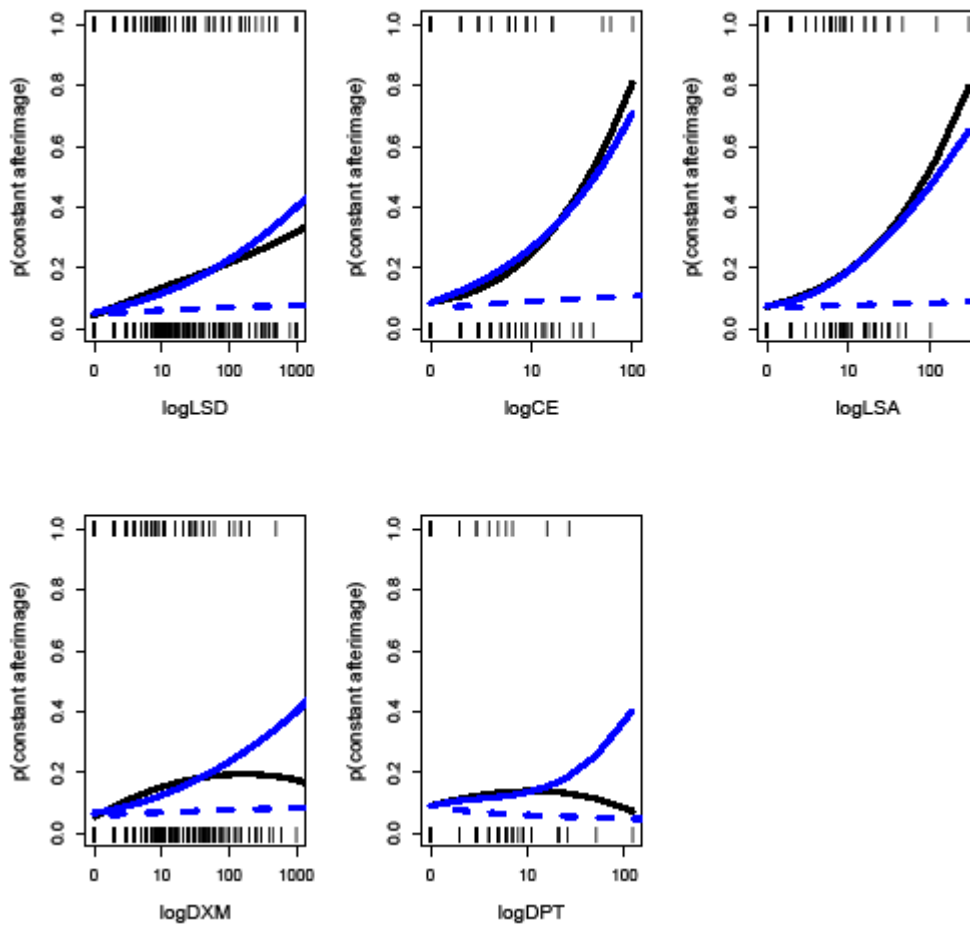


Figure 1.6: CONSTANT PATTERNS $\sim \log \text{LSD} + \log \text{DXM} + \log \text{CI} + \log \text{Datura}$

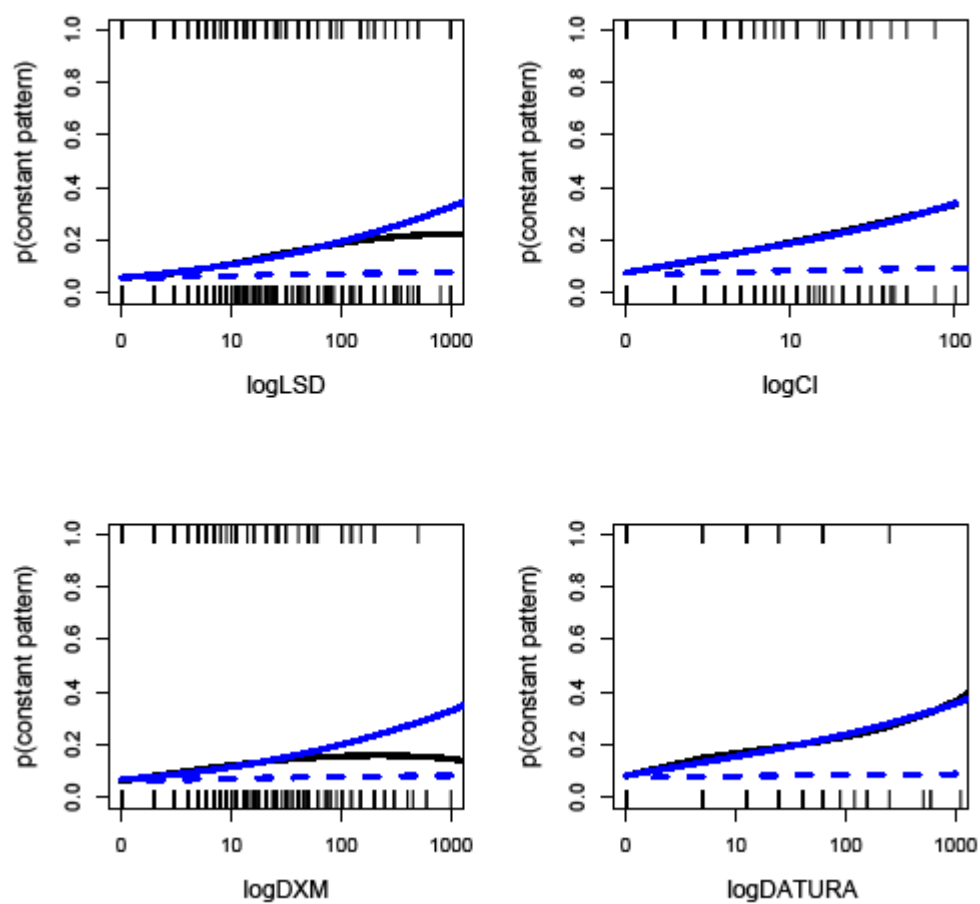


Figure 1.7: CONSTANT COLORS $\sim \log \text{LSD} + \log \text{DXM} + \log \text{CE}$

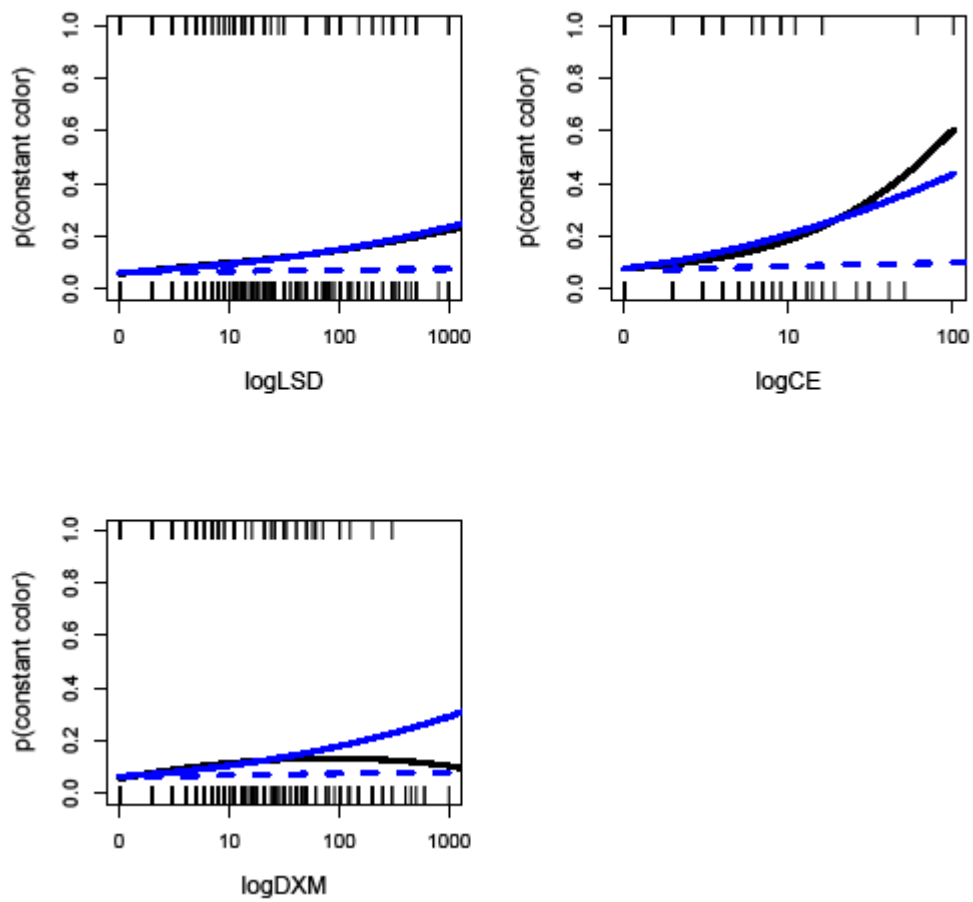
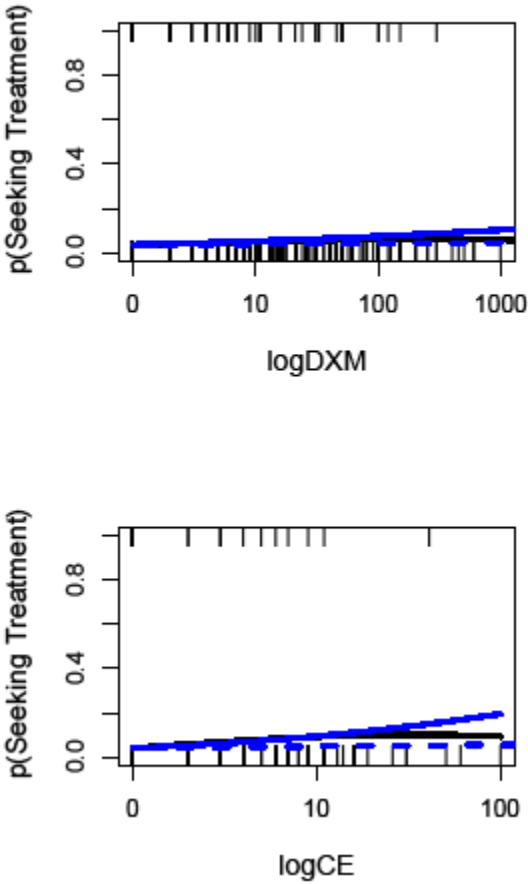


Figure 1.8: SEEK TREATMENT ~ Halo Constant + Move Constant + Patterns Constant + Thing Constant



CHAPTER 2: Mechanisms of Hallucinogen-Induced Visual Changes

In the previous chapter, I found that unusual drug-free visual experiences were prevalent in hallucinogen users who responded to an online questionnaire. Among other symptoms, geometric visual patterns were reported by 24.2% of respondents. In this chapter, I describe research on the mechanisms of visual hallucinations, which I investigated by measuring the perceptual effects of the hallucinogenic 5-HT_{2A}R agonist and 5-HT releaser 3,4-methylenedioxymphetamine (MDA) in a double-blind placebo-controlled study. I found that MDA produced a significant increase in closed-eye visuals (CEVs), with considerable individual variation. Magnitude of CEVs after MDA was associated with lower performance on measures of contour integration and object recognition, supporting a hypothesized link between hallucinations and impairments in sensory or perceptual processing. In contrast, I found only limited evidence that MDA might increase the magnitude of the tilt illusion, as predicted by Ermentrout-Cowan models of geometric visual hallucinations. Additionally, I was not able to confirm or discount changes in efficacy of top-down processing during hallucinations.

BACKGROUND

There is a long history of research on hallucinations, with reports by some of the luminaries of science and philosophy. Percepts produced by deformation of the eyes played a central role in theories of vision by Plato, Kepler, Descartes, Boyle, Newton and others [254]. Flicker-induced hallucinations were discussed by Purkinje [255] and Helmholtz [256]. Klüver and many other authors (e.g. [257, 258]) argued that the consistent patterns seen in different hallucinatory states implied that there must be a fundamental mechanism of the nervous system that supports them. Such a mechanism, Weil-Malherbe and Szara [259] wrote, must be concerned with the “organization of perceptual processes, especially those aspects of perception which normally allow us to see objects as permanent and stable things regardless of illumination, position, or distance” (p. 329). The implication of this is that research into hallucinations may be able to provide insights into the workings of normal perception and brain function.

I begin by defining and reviewing historical theories of hallucinations, advocating a pragmatic approach that does not seek to separate hallucinations from illusions. Next, I describe the phenomenology of drug-induced hallucinations and formal modeling of a subset of these hallucinations. Finally, I provide background information on the tasks I used to elucidate the mechanisms of MDA-induced hallucinations, as well as experimental hypotheses.

Hallucinations, illusions, and delusions

While descriptions of supernatural visions are almost as old as written history, the modern concept of the hallucination originates in the 19th century, when Esquirol coined the term [260]. Broadly speaking, a *hallucination* can be defined as perception in the absence of a stimulus. Authors have differed somewhat in the precise criteria proposed to distinguish hallucinations from other false perceptions and interpretations [260-263].

Common criteria for hallucinations include the following:

- (a) Occur in a conscious and awake state (in contrast to dreams)
- (b) Occur in the absence of external stimuli (in contrast to illusions or delusions)
- (c) Have qualities of real perception, such as vividness and location in external objective space (in contrast to thoughts and mental imagery)
- (d) Are not controllable (in contrast to mental imagery).
- (e) Are taken for reality (in contrast to pseudo-hallucinations)

In contrast to hallucinations, *illusions* are false perceptions that occur in the presence of a stimulus. However, fully distinguishing hallucinations from illusions (and other false beliefs or perceptions) can be surprisingly difficult. Hallucinations caused by intermittent photic stimulation clearly have a triggering visual stimulus, but it is one with a uniform spatial structure that does not predict the resulting visual percepts [257]. Hallucinations during migraine aura or photic stimulation can be influenced by visual input [257, 264]. Thus at least some hallucinations seem to have a triggering stimulus. In cases with hallucinating patients, it is often difficult or impossible to determine whether or not some stimulus precipitated a false percept. These difficulties have led to an old joke that neurologists distinguish hallucinations from illusions by placing them in different chapters of the textbook. Accordingly, some authors have used definitions of hallucination that blur the distinction between hallucination and illusion [264-266].

Hallucinations are also sometimes differentiated from *delusions*, false interpretations of reality (with presumably correct sensory perception). However, as with illusion, there is potential overlap between hallucination and delusion. To begin with, many delusions may be a secondary consequence of a person's attempts to understand anomalous sensory experiences. Furthermore, some delusions may themselves be strange perceptions. Corlett, Frith, and Fletcher [267] argue that delusions of control, in which someone believes that their actions are caused by outside forces, may in fact be strange perceptions rather than strange beliefs. Thus, delusions may be closely related to hallucinations in practice.

The difficulty of cleanly defining hallucination may partly arise from the fact that hallucinations do not necessarily represent a distinct process from normal perception. Rather, they may be merely a label applied to a subset of false perceptions. Contemporary cognitive science often describes perception as the result of a series of hierarchical interactions between top-down and bottom-up processes that attempt to predict the world based on past experience [268-270]. If perception is an inferential process, then the distinction between a false perception (hallucination) and a false inference (delusion) becomes difficult to maintain.

Similarly, illusions can be seen as a result of the fundamentally probabilistic nature of this inferential process. Perception involves an inverse problem: any stimulus may have been generated by many different real-world sources. A plausible solution to this problem is to generate percepts predicated on the probability distributions of the physical sources of sensory inputs [271-273]. Research analyzing the statistics of natural images suggests that visual illusions may be, essentially, a side effect of this inference [274-279]. Illusions

represent a best-guess interpretation of a statistically improbable physical source. Thus, even though the discrepancies between the illusory percept and source seem maladaptive, they result from a strategy that overall allows successful interaction with typical environments.

Given these theoretical points, and in the interest of simplicity, I will use the term hallucination inclusively throughout this document to include drug-induced pseudo-hallucinations and other visual changes in addition to proper hallucinations. In most cases, however, the phenomena produced by the serotonergic hallucinogens that I study (such as MDA) are not taken for reality, but are instead recognized as false perceptions caused by a drug. Thus, they would be technically classified as pseudo-hallucinations by many authorities.

Phenomenology of drug-induced visual hallucinations

The visual phenomenology of drug-induced hallucinations may provide insights into their mechanisms. Hallucinogens produce a bewildering variety of visual phenomena, often perceived with both open and closed eyes [159, 263, 280-284]. Form and depth perception may be unpredictably altered. Synesthesia is reported by approximately 30% of participants in LSD experiments [285-288]. Afterimages can be prolonged and may include positive afterimages [287, 289-291]. Motion perception impairments are common, including moving objects appearing as a series of still images and still objects appearing to move [292, 293]. In a rare controlled psychophysical study, Carter et al. [294] found that the hallucinogen psilocybin impaired a higher-level motion coherence task without significantly altering the threshold contrast at which the direction of a drifting grating could be discriminated. Despite this variety of visual changes, researchers have noted some striking commonalities in the visual effects of hallucinogens.

One such commonality is the temporal progression of visual changes. Drug-induced hallucinations increase in complexity and richness in the early part of an orally administered hallucinogen trip. Shanon [263] reviews scientific and anthropological attempts to categorize ayahuasca hallucinations, and then provides his own structural typology of five categories of increasingly complex ayahuasca visuals: *those without semantic content*; *primitive figurative elements*; *images*; *scenes*; and *virtual reality*.²

These categories may be best clarified by describing a hypothetical progression of hallucinations. For example, hallucinations may begin as perceptions of light *without semantic content*. These simple phosphenes may become elongated, and eventually organize into repetitive patterns, often in fluorescent colors. Such patterns usually have bilateral symmetry. At some point, these hallucinations without semantic content may give way to those with *primitive figurative elements*. Rapidly transforming shapes lose their geometric quality and bilateral symmetry, and begin to appear like unfamiliar animals. In time, imagery may become part of a larger percept made up of both geometric forms (typically three-dimensional), and figurative elements embedded in the geometric

² Shanon includes a additional category, visions of light, that is not part of this progression of complexity, to emphasize the perceived significance that percepts of light have throughout the drug-induced experience.

pattern. While the figurative elements in this stage lack independence or permanence, the next stage of *images* are increasingly stable and may appear as single objects or series of thematically related objects. These objects are followed by the appearance of *scenes*, which may initially appear like brief glimpses through keyholes but can come to occupy the entire field of view. These eventually may present narrative structures, as if the viewer is watching a film. These scenes can become so engrossing that one is effectively in a *virtual reality*, although one is typically still able to interact with the real world and other people.

These categories tend to occur in the order listed, although there is considerable trip-to-trip variation and individual categories are not always experienced. Shanon notes that this increase in complexity is accompanied by a sense of progression in other phenomenological categories, including progressions towards the figurative, increased stability of imagery, greater perceived richness of content, greater perceived psychological significance, and greater likelihood of spiritual impact.

It is unclear to what extent these progressions are inherent in the process of hallucination formation, or if they represent increasing concentrations of the hallucinogen in the brain. Reports of similar progressions in individuals experiencing migraine aura hallucinations [295, 296] suggest it may be partly a property of sustained hallucinations, with hallucinatory activity spreading into or stabilizing in different parts of the brain. However, an appropriate experiment creating steady-state concentrations of a hallucinogen and measuring phenomenology has not yet been performed.

The categories Shanon proposes build on the pioneering work of Heinrich Klüver [280]. Klüver studied hallucinatory phenomena caused by the serotonergic hallucinogen mescaline. Among the common aspects of hallucinations he identified, Klüver noted four types of visual patterns that seemed to elaborate and combine to produce many of the geometric visuals seen in the earlier stages of hallucinogen intoxication. These four 'form constants' are (a) lattices (e.g., grating, lattice, fretwork, filigree, honeycomb, and chessboard patterns); (b) cobwebs; (c) polar symmetric shapes (e.g., tunnel, funnel, alley, and cone patterns); and (d) spirals. These patterns have probably been studied more than any other type of hallucination (except perhaps the fortifications and scotoma of the migraine aura) and were independently re-discovered by Siegel in the 1970s as he conducted research with a variety of psychoactive drugs in trained perceivers [297, 298].

One reason that these patterns have been studied is their ubiquity. Simple geometric hallucinations can be produced by a variety of conditions in addition to drugs. Simple geometric hallucinations are seen in states such as hypnogogic hallucinations, insulin hypoglycemia, and fever delirium [280, 299]. Geometric hallucinations can also be produced by intermittent illumination (i.e., using a stroboscope or similar) or pressure on the eyes (often called deformation phosphenes) [300-305].

The hallucinations seen in these states are not necessarily identical. For example, color appears more likely to occur in drug-induced hallucinations than other types of hallucination [257]. A moving scotoma is a characteristic of migraine aura but not other hallucinatory syndromes. However, geometric hallucinations from different causes are

sufficiently similar that it is probable they share a common neural substrate. Furthermore, Billock and Tsou [257] assert that the hallucinations induced by migraine (presumably the fortifications), flicker, and mescaline all have a scale that suggests a cortical activation of about 2 mm, roughly corresponding to the dimensions of an orientation hypercolumn in primary visual cortex. One implication of this is that research into hallucinations may be able to provide insights into the workings of normal perception and brain function.

Theories of visual hallucinations

Hallucinations are usually explained by some combination of three factors, none of which are mutually exclusive.³ The first factor, *abnormally increased neural activity*, is emphasized in research on hallucinations in migraine and epilepsy. The second factor is *alterations in cognitive functions* such as filtering, attention, or inference. This type of factor is often emphasized in theories of dementia and psychosis. The third factor, *loss of sensory or perceptual ability*, is emphasized in release/deafferentation theories of hallucinations. In the following sections, I review these three factors and present available data related to drug-induced hallucinations.

Abnormally increased neural activity. In some cases, hallucinations appear to arise from abnormal activity in the cortex [306-310]. Abnormal excitatory activity is likely the mechanism of hallucinations in individuals with migraine or (temporal or parietal lobe) epilepsy [261, 309-312]. Studying these disorders or experimentally stimulating brain suggests that the contents of hallucinations depends on the neural site of abnormal activity and that a broad network of the brain needs to be activated for hallucinations to be perceived. Models of how hallucinogens might increase neural activity in primary visual cortex were first developed by Ermentrout and Cowan and are discussed below.

The neural basis of the migraine aura appears to involve a phenomenon called ‘cortical spreading depression’ (CSD) [309, 310]. CSD consists of a wave front of neural depolarization, suggesting that cortical visual areas in migraineurs have lowered thresholds for generating this form of excitatory wave [313, 314]. It is a matter of ongoing research whether this abnormal excitation is ultimately due to increased excitatory mechanisms or weakened inhibitory mechanisms. Studies using transcranial magnetic stimulation [315-318], functional magnetic resonance imaging (fMRI) [319-321], electrophysiology [322-324], and psychophysics [325-327] generally support the concept of weakened inhibition, although findings are not uniform [327-334].

The resulting migraine aura has diverse phenomenology. It frequently appears as a growing blind spot (scotoma) surrounded by characteristic scintillating and predominantly black and white angled lines, which resemble an overhead view of the walls of a fortress [335]. Herschel [258] hypothesized that his migraine aura might be due

³ Psychoanalytic theories of hallucination do exist, including Savage’s theory that hallucinogens cause regression to childlike primary process thinking [259, 304, 305]. Although the specific contents of thoughts and experiences during hallucinogen-induced altered states can undoubtedly be interpreted using psychoanalytical methods and theories, such matters are outside the scope of this dissertation and will not be discussed.

to “a kaleidoscopic power in the sensorium to form regular patterns by the symmetrical combination of causal elements”. Indeed, the fortification lines commonly seen during migraine aura appear to be a result of CSD in primary visual cortex propagating through orientation-selective neurons in hypercolumns [336]. However, the phenomenology of migraine aura is diverse and can include complex visual hallucinations, alterations of touch and smell, impairments of speech, and disordered ideation [295, 296]. These phenomena can be hypothesized to be the result of unusual neural activity occurring in locations other than primary visual cortex.

In fact, a substantial body of research attempts to link the specific content of hallucinations to differences in the locations of abnormal activity. This has been primarily studied by either stimulating the brain directly or by conducting functional imaging studies of individuals having hallucinations. These studies are reviewed below.

Early brain stimulation work by Penfield and Perot [308] suggested that electrical brain-stimulation produced hallucinations whose modality, content, and complexity depended on the stimulation site. For example, primary auditory-stimulation led to the experience of noises, while secondary association cortex-stimulation induced perception of complex sounds and right superior temporal gyrus-stimulation produced musical hallucinations.

However, unlike Penfield’s reports, later research suggests that hallucinations require activation of a larger neural assembly than the stimulated section of cortex [337-339]. Most subsequent researchers have found that experiential responses are mainly produced by stimulating limbic structures such as the hippocampus and amygdala, rather than the neocortex. For example, Halgren et al. [338] reports that of 3495 stimulations of the medial temporal of 36 patients with epilepsy, only 7.6% produced the sort of experiential responses reported by Penfield and colleagues. In contrast, stimulation of limbic structures reliably leads to reports of simple phosphene-like percepts (lights, flashes, streaks) or complex visual experiences of persons (including autoscopic experiences), scenes, or objects [337-339]. Interestingly, hallucinations only appear to be elicited when sustained neural activity (after-discharges) occurs after the stimulation [339]. It appears that the actual production of hallucinations during electrical brain-stimulation may usually result from interactions between neocortical and limbic systems (and possibly other systems), rather than simple activation of a group of cortical neurons encoding a memory.

In the last 15 years, researchers have used functional imaging to identify neural correlates of hallucinations. Many of these studies involve auditory hallucinations in schizophrenia and find significant activations in auditory cortex, language areas, and limbic areas [340-342]. Studies of visual hallucinations in Parkinson's disease [343], Charles Bonnet syndrome [344], and schizophrenia [342, 345] find activation of higher visual areas associated with object and scene perception. However, only one study to date has used a localizer paradigm to map brain areas that respond to specific visual stimuli in the hallucinating participant. Oertel et al. [345] studied a schizophrenic with frequent visual hallucinations, making functional magnetic resonance imaging (fMRI) measures of eight hallucinatory episodes involving people, objects, and scenes during a single data acquisition session. In a separate fMRI session, the researchers used a localizer program

to map the fusiform face area (FFA), the occipital face area (OFA), extrastriate body area (EPA), and parahippocampal place area (PPA). They detected increased activity during hallucinations in bilateral PPA and left EPA, while the activation in the right fusiform gyrus was posterior to the FFA and closer to the OFA. The researchers also observed activity in the left inferior temporal/middle occipital gyrus (the lateral occipital complex), which is believed to be important for view-independent object representation [346]. Interestingly, these higher visual areas were activated without significant changes in the primary visual cortex, consistent with predictive coding models of vision [347]. Prefrontal increases, as occur during active visual imagery, were also not detected [348]. In addition to these visual areas, hallucination-related changes were seen in memory-related (posterior cingulate, hippocampus) and attention-related (superior parietal, precuneus) areas.

In contrast to studies of migraine, Charles Bonnet syndrome, and schizophrenia, there is a lack of human studies of the mechanisms of drug-induced hallucinations. However, substantial work has been done to model geometric hallucinations. Ermentrout and Cowan [87] first proposed neural mechanisms for geometric hallucinations. Assuming that these patterns were produced in the primary visual cortex, they modeled the dynamics of interacting populations of excitatory and inhibitory neurons using Wilson-Cowan equations. They found that spatially periodic patterns can form by a process analogous to that used by Turing [349] to explain the formation of stripes and spots on animal coats. Turing determined that complex patterns can be formed if at least two chemical species that affect the production of pigments in different ways diffuse at different rates. This creates the so-called Turing instability and resulting patterns. Such theories have been applied not only to explain phenomena such as patterns on seashells [350] but also spatial patterns of diseases and animal populations [351].

Ermentrout and Cowan realized that, after correcting for the logarithmic spatial transformation that occurs between retinal and primary visual cortex representations [352-354], many of the patterns described by Klüver could be explained by gratings of activity in primary visual cortex with different orientations. Thus, lines of activity on the cortex may appear as bull's-eye patterns or fan shaped patterns depending upon orientation on the cortex.

In their model, Ermentrout and Cowan proved that, if there is sufficiently increased excitation, cortical networks of excitatory and inhibitory neurons can produce spontaneous patterns in the form of parallel stripes of neural activity. These stripes may then intersect with other stripes to form more complicated textures. This pattern formation can be achieved in three ways: by increasing excitation, by decreasing inhibition, or by adding spatially uniform input.

These three possibilities have been explored in models by different researchers. While Ermentrout and Cowan increased the weight of excitatory coupling to model the case where excitation was increased in individuals under the influence of mescaline, Tass [355, 356] modeled pattern production when inhibition was decreased, as may occur in the case of epileptic hallucinations. Hallucinations produced by increasing input, such as those seen during flicker-induced hallucinations or during deformation phosphenes are

discussed by Billock and Tsou [257]. The same authors also point out that, as predicted by these models, conditions that lead to pattern formation appear to have additive effects. For example, stroboscopic stimulation rapidly produces mescaline-like visuals in individuals who have been given subthreshold doses of mescaline, as demonstrated by Smythies [357]. Finally, it should be mentioned that anisotropic connections in a neural network – such as spatial-orientation-selective connections – can lead to a greater variety of patterns, such as textures superimposed on geometric structures [358, 359].

Testing abnormal-excitation theories of drug-induced hallucinations using the tilt illusion. Some hallucinatory conditions show a link between contents of hallucinations and abnormal excitation in different brain areas. Geometric hallucinations, for example, may be the result of increased neural excitation, specifically reflected in altered lateral interactions in orientation-selective neurons in primary visual cortex. I selected the tilt illusion (TI) to investigate this possible phenomenon. Although many visual phenomena are thought to depend on orientation-selective neurons, few are as robust as the TI, which can be convincingly demonstrated in single trials. In addition, many other potential measures rely on low contrast stimuli and are therefore likely sensitive to possible drug-induced changes in pupil size. Finally, there are close links between formal models of geometric visual hallucinations and models of the tilt illusion. For these reasons I used the TI.

The TI is a widely-studied orientation-based visual illusion. The TI occurs when viewing a test line or grating against a background or surround of similar stimuli with a different orientation from the test stimulus. This causes an orientation-dependent shift in the perceived orientation of the central test stimulus, as illustrated in **Figure 2.1**. Factors that affect the magnitude of this shift include presence of a frame around the grating and the duration of presentation [360, 361]. The TI is usually a few degrees in magnitude and peaks when the difference between the test line and inducing grating is near 15° , with lesser illusions perceived over 0 to 50° .

The tilt aftereffect is a visual phenomenon that is closely related to the TI. In the tilt aftereffect, prolonged viewing of a tilted test stimulus alters perception of the orientation of a subsequent stimulus [2, 3]. Like the TI, the effect can be perceived when orientation differences between the adapting and test stimuli are up to 50° , and the phenomenon is also maximal at approximately 15° difference.

The TI and tilt aftereffect are of theoretical interest because they demonstrate the extent to which local detection of contours can be influenced by information from distant points of the visual field. A common explanation is that the TI is the result of lateral inhibition between orientation selective cortical neurons in the occipital cortex [362, 363]. Resulting changes in the tuning curves of these neural populations may underlie observed contextual influences on perception in the TI (and tilt after-effects) [364-368]. Bressloff and Cowan [369] and Yang [2] have developed formal models of primary visual cortex that reproduce the TI. In **Figure 2.2**, I illustrate the TI as reproduced by a Matlab implementation of the model by Yang. In this winner-takes-all neural population, orientation selective neurons are assumed to excite nearby neurons with similar orientation selectivity and inhibit nearby neurons with different orientation selectivity.

Increasing the strength of lateral interactions between orientation-selective neurons in primary visual cortex, as represented by parameter E, increases the magnitude of the TI.

Because they reflect the interactions of occipital cortical neurons, these visual phenomena can be a useful probe of the potential acute and chronic effects of hallucinogens on early cortical vision. Indeed, one study has examined the effects of serotonergic manipulations on the tilt aftereffect, and two studies have reported alterations of the tilt aftereffect in MDMA users. A study by Masini et al. [370] used acute tryptophan depletion (a dietary manipulation that temporarily depletes central 5-HT) and detected a significant increase in the magnitude of the tilt aftereffect (with mean perceived vertical shifting from 0.43 to 1.07° after adaptation) using an adaptation angle of 15°. Brown et al. [371] reported an increased tilt aftereffect in a subset of ecstasy users (those who had not recently used amphetamines) and Dickson et al. [372] confirmed this finding in a study that attempted to control for use of other drugs. Thus, orientation illusions such as the TI and tilt aftereffect may be sensitive to serotonergic manipulations.

Cognitive theories of hallucinations. Cognitive theories have generally sought to explain hallucinations in terms of impaired control of information flow, such as altered gating of information or altered balance of top-down and bottom-up information processing [373, 374]. In recent years, theories emphasizing the role of inference in perception [267] have been replacing filter-based metaphors [375]. Thus, altered balance of top-down and bottom-up information has been increasingly described as an impairment in inference that produces a bias to confirm predictions.

Early cognitive theories of drug-induced hallucinations emphasized altered gating or filtering of information. One motivation for this was a study by Bradley and Elkes [376], which found that environmental factors (such as ambient sound) played a greater role in the electroencephalographic changes induced by LSD than those induced by amphetamine and most other pharmacological agents. Weil-Malherbe and Szara [259] state that this finding led to the theory that serotonergic systems might selectively filter or gate sensory inputs (and thereby possibly “link affect with perception and meaning with experience”). Subsequent studies on cats showed that hallucinogens did indeed decrease habituation to nonreinforced stimuli (e.g., [129]). More recent electrophysiology studies in rats suggest that serotonergic 5-HT_{2A}R may have gain-control functions in layer V pyramidal cells [88], which seems consistent with the theory of serotonergic filtering.

A modern-day descendent of these theories is Vollenweider and Geyer’s proposed cortico–striato–thalamo–cortical loop model of the brain and hallucinogen effects [110, 377]. They suggest that hallucinogens impair an attentional gating mechanism that normally acts on the thalamus, which then causes excessive interoceptive and exteroceptive information processing. This leads to a breakdown of cognitive integrity and to difficulty distinguishing self from non-self. Impaired thalamic filters have been modeled in animals using the prepulse inhibition paradigm [378–380], and have been used as an explanation of schizophrenia [381].

Closely related to the idea of impaired filtering is that of impaired attention. Attention is sometimes described in terms of changing the selectivity of cells for features — a

filtering effect — as in the biased competition model of Desimone and Duncan [382-384]. Attention is also sometimes described as having gain control effects, and neurophysiological studies find that attention can cause multiplicative enhancements in response rates to attended stimuli [385, 386]. Impairments of this gain control could potentially lead to either of the other two hypothesized contributions to hallucinations: decreased sensory fidelity or abnormal activity. In their Perception and Attention Deficit model, Collerton et al. [373] argue that both attention and perceptual deficits are necessary for recurrent complex visual hallucinations. They support this theory by demonstrating statistically significant relationships between the frequency of visual hallucinations and the severities of both perceptual and attentional impairments across five different neurodegenerative and dementing illnesses [387].

Recent theories have described hallucinatory phenomena as the result of a failure in inference rather than filtering [267, 388-390]. These theories see perception as "unconscious inference" [391], which involves a hierarchical series of processes that progressively transform and abstract sensory information. At each level of processing, bottom-up information from a previous level is transformed based on top-down influences (such as predictions and attentional biasing) from hierarchically higher levels. Hallucinations result from excessive weight being assigned to top-down factors rather than bottom-up information, which may be noisy or unpredictable [374, 392].

It is worth noting that some theories have been developed that hypothesize specific impairments in inference to explain psychosis. These seem less relevant to drug-induced visual changes. For example, source-monitoring theories explain hallucination as the erroneous attribution of internally generated information to an external source [393-395]. Collerton et al. [373] point out this theory's apparent difficulty accounting for the fact that about half of the patients seeing complex hallucinations are aware that they are hallucinations. As noted earlier, most individuals on serotonergic hallucinogens retain awareness that their visions are drug-induced. Thus, it is difficult to see how source-monitoring errors could account for drug-induced hallucinations.

Testing cognitive theories of drug-induced hallucinations using cue-induced changes in image recognition. Potential drug-induced alterations in balance of top-down and bottom-up information processing have been studied using binocular depth inversion. Binocular depth inversion refers to the phenomenon in which stereoscopic information is presented with the normally left-eye view delivered to the right eye and vice versa. This causes images of convex objects to have cues that they are concave. Nonetheless, healthy volunteers typically still perceive the images as convex. If this is due to the domination of top-down prior object knowledge over bottom-up data, then it can be used to test for impairment of top-down processing in different populations. However, although studies with oral THC and other cannabinoids [396-398] found drug-induced changes, administration of two different doses of (S)-ketamine failed to reduce or otherwise alter the inaccurate perception of binocular depth inversion [399]. Similar studies have not yet been carried out with serotonergic hallucinogens. One limitation to this task is that top-down knowledge is normally so dominant in this illusion that drug-induced increases in top-down efficacy would presumably not be detectable due to a ceiling effect except under the most severe conditions.

An alternative method is to provide top-down cues for recognizing images. This is an approach I take here. Appropriate top-down knowledge can enable recognition of an object from an otherwise unrecognizable degraded image [400-402] and, more generally, context facilitates object recognition [403-405]. For example, performance in a rapid serial visual presentation (RSVP) paradigm is improved by more accurate descriptions of target stimuli [406], and participants who are told the gist of stimuli perform better in an old-new recognition task [407]. To assess possible changes in balance of top-down and bottom-up information, we used a task in which participants must recognize degraded images of common objects. Participants were shown cues (the names of objects) before being shown degraded images that they were asked to identify. In such a task, accurate cues should improve recognition performance and inaccurate cues potentially decrease performance. If the mechanism of drug-induced hallucinations involves increased efficacy of top-down influences of perception, then there should be drug effects on both true and false cues, widening differences in accuracy. The drug-induced increase in top-down influence should improve recognition of degraded images when true cues are given but impair recognition when cues are false. Alternatively, weakened top-down influence should reduce this cueing effect.

Loss of sensory or perceptual ability. Clinical and experimental research has shown a robust link between hallucinations and decreased sensory or perceptual accuracy. A common explanation for this association is that a lack of sensory input facilitates a cortical release of representations. The first theory of release or disinhibition was proposed by Hughlings Jackson [408]; it was then extended to include LSD-induced hallucinations by West [119], based on nonhuman primate research from Evarts [409]. The essential idea is that, under normal conditions, representations (and/or memories, depending on the theorist) are suppressed by a mechanism that regulates the flow of information in the brain. Input of new information also inhibits these representations from emerging into awareness. If the input is decreased and the individual remains sufficiently aroused to retain awareness, released representations may be dynamically organized and experienced as hallucinations. Evidence for this theory, briefly reviewed below, comes from both individuals with visual impairment and from healthy participants in sensory-deprivation experiments.

Many individuals with visual impairment develop visual hallucinations. When other psychiatric or neurological diagnoses cannot be made, this phenomenon is called Charles Bonnet syndrome. Reported prevalence in different samples with visual impairment varies widely, from as little as 0.4% to as high as 17.5%, and it may be under-diagnosed [410-412]. Charles Bonnet syndrome hallucinations often feature scenery, people, animals, buildings, and/or plants. They appear in alert open-eyed individuals without obvious triggers, and typically last for seconds before disappearing [413-415]. There has been debate as to whether cognitive impairment is a risk factor or precondition for Charles Bonnet syndrome. Indeed, ffytche [416] notes that some risk factors for hallucination (such as older age, lower cognitive performance, and living alone) may relate to risk of dementia.

Sensory-deprivation experiments, however, have demonstrated that hallucinations can be readily induced in seemingly normal individuals, and are consistent with release theories

of hallucination [417-419]. For example, Merabet et al. [419] reported that ten (77%) of 13 participants described visual hallucinations that generally began between 24 and 48 hours after being blindfolded. These hallucinations were either simple or complex, had sudden onset, vanished spontaneously, and seemed unrelated to the alertness of the individual. The hypothesis that these hallucinations may result from a "release" of cortical processing is further supported by a study using both fMRI and transcranial magnetic stimulation to demonstrate increased visual cortex excitability within minutes of visual deprivation [420].

Across many conditions, poor vision is a consistent risk factor for developing visual hallucinations. Acuity (the ability to discern detail) was identified as a significant or trend-level risk factor in six out of the nine studies reviewed by ffytche [416]. Similarly, Jackson et al. [421] assessed a consecutive series of 225 patients (35% of whom reported visual hallucinations) at a low-vision rehabilitation clinic, and found that contrast sensitivity (the ability to discern shades of grey) may be a more sensitive measure of hallucination risk than visual acuity. Furthermore, reduced contrast perception in Parkinson's disease is also associated with visual hallucinations [422-425].

In addition to these relatively low-level visual functioning measures, there is evidence associating decreased higher-level perceptual organization with hallucinations. Object and visual space perception are impaired in Parkinson's disease patients with visual hallucinations compared to those without [426-428]. Individuals at high risk for psychosis have been reported to have deficits in visual form perception that predate the first onset of psychosis [429]. Schizophrenia is associated with extensive visual impairments, with some evidence suggesting great impairment in higher-level than lower-level visual processing [430]. Among many other deficits, impairments in contour detection are seen in individuals with schizophrenia [396, 431-435], which is an effect that can also be seen in people under the influence of the NMDA antagonist hallucinogen ketamine (e.g., [436]).

Testing sensory/perceptual-impairment theories of drug-induced hallucinations using contour integration. Overall, there appears to be a strong link between decreased sensory or perceptual ability and hallucinations. If this is a factor in drug-induced hallucinations, then one would predict that performance on visual perception tasks would be impaired by hallucinogens. Furthermore, one would predict that individuals with lower baseline performance on these tasks should have increased susceptibility to drug-induced hallucinations. I chose to measure perceptual ability with two tasks: contour integration and object recognition. Contour integration is discussed immediately below. Object recognition has been previously introduced.

To arrive at a unified percept of a visual object, the brain integrates the output of local analyzers that respond to different parts or features of that object. One aspect of this process may be the identification of contours. The conditions that lead individuals to perceive contours have been extensively studied [437-439]. Results are consistent with the Gestalt principle of "good continuation" [440] in which discrete contour elements positioned and oriented in a smooth path are readily grouped together. The psychophysical properties of contour perception suggest the existence of what Field,

Hess, and Hayes [437] called the “association field”. This term describes the hypothesized phenomenon of mutual facilitation between neurons that respond to orientations that correlate in a manner suggesting a contour, with mutual inhibition between neurons that encode elements whose orientations vary randomly.

This integration has been often studied using tasks that involve the detection of spatially extended patterns of Gabor gratings obscured by orientation jitter and a background of randomly oriented Gabor gratings [437-439] (**Figure 2.3**). Perceiving these spatial patterns requires both local orientation analysis, as might be carried out by individual V1 neurons, as well as integration of these local analyzers, likely by lateral interactions among neurons and feedback from higher visual areas. Integration is required for two reasons. First, the spatial patterns are too large to be detected by purely local filters. Second, because they are hidden by randomly oriented Gabor gratings that eliminate density cues, the spatial patterns cannot be detected by neurons with large receptive fields corresponding to the size of the contour. Thus, the long-range lateral and feedback interactions enabling spatial integration and perceptual organization can be isolated and measured with this task.

In addition to the above theoretical arguments, empirical data from animals and humans suggest that successful perception of contours in this task may depend on integration of information in early visual cortex [441-443]. Animal electrophysiology studies demonstrate that gratings outside the classical receptive field of a neuron can alter the neuron’s firing rate when an appropriately orientated grating is placed in the receptive field [444]. These changes seem to roughly correspond to effects seen in analogous psychophysical studies in humans [445-447]. Li, Piëch, and Gilbert [448] used receiver operating characteristic analyses of V1 neuron responses to demonstrate that these neurons encoded the presence or absence of a contour as reliably as behavioral responses in primates that were trained to detect contours. Thus, there is an impressive correspondence between theoretical arguments and psychophysical and physiological data.

Accordingly, contour integration appears to rely on neural interactions in early visual cortex, including V1. A contour integration task was therefore selected to test the hypothesis that relatively low-level measures of perceptual organization would be impaired by MDA and that poor perceptual organization would be associated with greater visual changes. I also selected this task because I thought it important to choose a task that could detect drug-induced improvements as well as impairments. Although lower perceptual ability is linked to hallucinations, hallucinogen users sometimes report subjective feelings of improved perceptual ability during acute drug effects [186, 449], and signal detection approaches to hallucinations suggest that some changes (liberal criteria in object detecting filters) might not only lead to hallucinations (false alarms) but also better perception of weakly indicated stimuli [375].

Hypotheses. I predicted that MDA would induce self-report closed-eye visual hallucinations (closed-eye visuals, CEVs). Given the formal models linking hallucinations and tilt illusion, I predicted MDA would also increase the magnitude of tilt illusion. The two other perceptual tasks were designed to test the hypotheses of

relationships between hallucinations and impaired perception (contour and object recognition tasks) and altered efficacy of top-down information in perception (object recognition task).

METHODS

General study design for MDA experiment

This double-blind, placebo-controlled clinical study was carried out in a hospital setting using twelve healthy volunteers who were admitted into the research ward for the duration of the study. Extensive safety monitoring was carried out before and after, until drug effects resolved. Participants returned to the laboratory two weeks after discharge to ensure residual toxicity was not present.

Participants were individuals with self-reported experience with either MDA alone or experience with both MDMA and a hallucinogen, such as LSD. Demographics are described in **Table 2.1**. None had any DSM-IV drug dependence diagnoses (other than nicotine or caffeine). Comprehensive safety screening procedures included health & physical, self-report drug history, 12-lead EKG, liver panel, and blood chemistry. Participants were asked to practice effective contraception during the study. Pregnancy and drug toxicology tests were performed before drug administration.

Experimental drug administration occurred after a 2-hour fast to minimize individual variance in drug absorption. Lactose in a gelatin capsule was used for the placebo. MDA was administered in a dose of 98 mg/70 kg body weight in a gelatin capsule identical to the placebo. Drug and placebo dosing occurred on consecutive days.

Timed measurements included blood samples for pharmacokinetic purposes, physiological measures of heart rate and blood pressure, self-report measures of drug effects, and computerized tasks. Only measures relevant to visual changes are described in this chapter. Additional emotion and attention measures are described in the next.

Self-report measures

Self-report measures of overall drug effects were the visual analog items “any drug effects”, “good drug effects”, “bad drug effects”, and “high”. Self-report measures of drug-induced visual changes were the visual analog items “when I close my eyes I see complex abstract patterns” (hereafter shortened to ‘patterns’), “when I close my eyes I see objects or non-living things” (‘things’), “when I close my eyes I see animals, people, or beings” (‘beings’), and “when I close my eyes I see places or landscapes” (‘scenes’). Participants used the mouse to slide a mark along a line that was labeled at the left and right extremes with the phrases “Not at All” and “Extremely”, respectively. Participants closed their eyes for 30 seconds before answering the visual questions. This interval was timed by computer, which provided an auditory cue to re-open the eyes. Self-report measures were made before drug administration and at 0.5, 1, 2, 2.5, 3, 4, 6, and 8 hours after drug administration. Maximum post dose changes (E_{max}) were used as the primary outcome measures. In order to examine relationships with other outcome measures,

summary measures of peak overall drug effects and peak visual changes were made by averaging Emax for the four questions in each of those two categories.

Tilt illusion task

To estimate the strength of the Tilt Illusion, I had participants determine if a two-dimensional, contrast-varying sine wave within a circular window was tilted to the left or right. I then varied the orientation of a surrounding grating, which changed the magnitude and direction of the tilt illusion. I determined the point of subjective verticality twice (using two one-up-one-down staircases with 0.5° step sizes) for each of the following surround orientations: -40° , -30° , -20° , -15° , -10° , 10° , 15° , 20° , 30° , and 40° . Three staircases without any surround were included to establish a baseline subjective vertical. Interwoven staircases terminated after six reversals and point of subjective verticality was estimated as the average of the last four reversals.

Participants were tested binocularly, seated approximately 0.110 m away from a 19 in. Dell monitor in a dimly lit testing room. Monitor resolution was set to 1024 x 768 pixels. Each trial began with a 500 ms mask circular stimulus composed of noise (which had an amplitude defined as a function of spatial frequency, using the formula $1/F^2$) intended to decrease any effects of previous trials. This was replaced by the target and, if present, the surround, both of which were presented until the participant made an untimed judgment about whether the central target was tilted left or right. Target was 1.2° diameter. Surround was 5.2° diameter. Both were 1.7 cpd. Sample stimuli are shown in **Figure 2.1**.

For each administration of the task, I determined mean points-of-subjective-verticality (PSV) for each surrounding orientation and then corrected for variation in head angle by subtracting the mean baseline ‘no surround’ PSV. The magnitudes of the tilt illusion for individuals and conditions were then estimated by taking the difference between the minimum and maximum PSV.

Contour integration task

I used a contour integration task to measure perceptual organization. Stimuli were closed chains of Gabor gratings in an egg-like shape that was obscured by a background of evenly-spaced randomly-oriented Gabor gratings (**Figure 2.3, left**). The egg-like shape pointed left or right and participants made an unspeeded two-alternative forced-choice (2AFC) about the shape’s orientation using a keyboard. Different levels of difficulty were created by varying the orientation jitter of the background distracter gratings.

The carrier spatial frequency of the Gabor gratings was 5 c/deg and their contrast was 95%. Space between contour gratings was eight times the wavelength of the Gabor gratings. Average spacing of distracter background gratings was 90% that of contour gratings. Spacing of contour gratings and the average spacing of distracter background gratings were kept constant.

Participants were tested binocularly, seated approximately 0.11 m away from a 19 in. Dell monitor in a dimly lit testing room. Monitor resolution was set at 800 x 600 pixels. Images subtended 9.4° of visual angle vertically and 12.4° of visual angle horizontally

from the testing distance. Stimuli were presented for 2 seconds. A fixation point on a gray background was shown at the beginning and end of after each trial. Images were presented in five blocks of increasing orientation jitter, varying between 7° and 24° across the five difficulty levels (7–8°, 11–12°, 15–16°, 19–20°, 23–24°). There were twenty trials in each block. Due to a computer error, the 23–24° jitter difficulty level was repeated in nine participants. These extra measurements were included in the analysis.

To analyze contour integration results, I used a generalized linear model with the 2-AFC logit function from the *Psyphy* R library to individually estimate a psychometric function for each subject and session [450]. Threshold (defined as 75% accuracy) orientation jitter was then used as the dependent measure in statistical models.

Object recognition task

This test was designed to assess both perceptual organization and hypothesized impairments in ability to use top-down information to facilitate recognition of drawings. Stimuli were black-and-white drawings of objects placed on a random noise background. Images were modified from the Rossion and Pourtois [451] set of images, which were developed as a copyright free and improved alternative to the commercial Snodgrass set. Images converted to black-and-white and all placed on an identical 288 x 288 pixel $1/F^2$ noise background, which was chosen to approximate the spectral characteristics of natural scenes [452].

To vary difficulty in a controlled fashion, I used the Random Image Structure Evolution (RISE, [402]) technique to progressively distort the images. Images were first subjected to a two-dimensional fast Fourier transform. The amplitudes of all images were averaged together. This mean amplitude was then used in place of the original amplitude for each picture and recombined with each picture's phase information. Reverse fast Fourier transforms were used to reconstitute the images. These reconstituted images all had the same frequency spectrum and differed only in phase. Thus, potential low-level differences between images were minimized. In order to degrade the images, I progressively shifted the phases of each image to/from the mean phase in steps of 5%, taking precautions to avoid zero crossings that would produce discontinuities. Four levels of image degradation are illustrated in **Figure 2.4**.

Pilot recognition experiments were conducted in 10 healthy volunteers in order to identify images that were particularly easy or difficult to identify. 120 images were retained for use. These were divided into six groups of comparable difficulty, which were counterbalanced across participants with respect to drug condition and cue type.

The task, which required approximately 40 minutes, included 60 images at each administration. Equal numbers of images were presented in three cueing conditions: true cues (the correct answer); false cues (a wrong answer); or no cue. Thus, cues were correct half of the time.

The task was administered at 3 hours after dosing. Participants were tested binocularly, seated approximately 0.11 m away from a 19 in. Dell monitor in a dimly lit testing room. Monitor resolution was set to 1024 x 768 pixels. Stimuli were presented for 2 seconds. A

fixation point on a gray background was shown at the beginning and end of after each trial.

Participants initiated each trial by pressing a key. Each trial then began with a cue. The cue consisted of a word (or a series of thirteen X characters, in the case of a no cue trial). After 1 second, the image stimulus was added below the cue. After 2 seconds, the cue and image disappeared and a question appeared asking if the participant could identify the image (“Do you know what it was? Y or N?”). If the participant did not believe they could identify the image, it was shown again in the next trial at a lower level of degradation. Images were initially shown with 87.5% distortion and decreased by 5% until participant reported they could identify the image or 12.5% distortion was reached. They or the researcher then typed in the named object. After this, the correct name and an undistorted version of the image appeared. The primary outcome measures of this task were recognition accuracy and level of distortion at which participants thought they could identify images. These were calculated separately for each cue type.

Statistical Analysis. Data were analyzed using mixed-effects models in R [241] with drug condition as a fixed-effect and participant as a random effect using a 2-tailed 0.05 level of significance. In order to control for possible sequence effects, linear models initially included a dummy-coded term for dosing sequence and a sequence-condition interaction term. When repeated measures were made (as in the case of self-report measures), data were transformed into maximum effects (Emax) for analysis. Summary statistics for the fixed-effects part of the model were calculated with the anova function in R. After a significant F-test, pairwise comparisons were made using Tukey’s post hoc tests.

RESULTS

MDA was well tolerated by all participants and produced psychological effects consistent with hallucinogenic action along with robust physiological changes. Participants frequently reported euphoric mood, altered sense of reality and time, and feelings of awe and contentedness.

Self-report measures

MDA had significant effects on participants’ maximum ratings (Emax) of all four general drug effects measures: any drug effects ($t = 18.624$, $p < 0.001$); bad drug effects ($t = 2.366$, $p = 0.0272$); good drug effects ($t = 9.769$, $p < 0.001$); and high ($t = 13.35$, $p < 0.001$). Individuals’ responses averaged across these four questions are plotted for the two conditions in **Figure 2.5**. To provide an indication of the contribution of the four questions to these means, **Figure 2.7** depicts the average response for each of the four questions during the MDA condition.

MDA produced significant closed-eye visuals (CEVs) in approximately half the participants. CEVs were generally absent during the placebo session, with the exception of one participant (3496), who reported seeing beings and landscapes. As a result, there were significant effects of dosing condition on participants’ Emax for all four visual questions: closed-eye patterns ($t = 4.437$, $p < 0.001$), closed-eye objects ($t = 3.883$, $p <$

0.001); closed-eye beings ($t = 2.54$, $p = 0.019$); and closed-eye scenes ($t = 2.79$, $p = 0.011$). Individuals' responses averaged across these visual questions are plotted in **Figure 2.6**. This variation in CEVs was probably not just due to variation in overall drug effects, as there was no correlation between mean E_{max} for visual questions and mean E_{max} for overall drug effects. There was also no significant effect of dosing sequence. **Figure 2.8** depicts the average response for each of the four CEV questions during the MDA condition.

Because anthropological evidence suggests that abstract visuals such as patterns occur before semantically-meaningful visuals during hallucinogen inebriation [263], I examined whether time of maximum change varied between patterns and other categories. However, a linear mixed-effects model comparing the time of maximum change between questions for the six individuals reporting the greatest visual changes was not significant.

Tilt illusion task

One participant had unusable data on their first session (placebo) because they misunderstood the direction of the judgments being made, preventing the staircase from functioning.

The magnitude of the tilt illusion was not significantly affected by dosing condition ($F_{1,9} = 2.515$, $p = 0.147$), but there was a significant effect of dosing sequence ($F_{1,9} = 6.658$, $p = 0.030$) in a mixed-effects model containing the two terms and their interaction. Individuals who received MDA first showed larger tilt illusions than those receiving it second (average magnitude for both sessions was 10.5 degrees vs. 7.0 degrees), consistent with potential residual effects increasing the tilt illusion on their day 2 placebo session (**Figures 2.9 and 2.10**). I therefore made a model where dosing condition predicted the tilt illusion in session one only. There was a significant effect of dosing condition ($F_{1,9} = 7.495$, $p = 0.023$), with MDA increasing the tilt illusion over placebo (11.3 degrees vs. 6.8 degrees).

There was no significant effect of peak CEVS on magnitude of the tilt illusion. Similarly, there was no significant effect of peak geometric CEV when this self-report item was analyzed separately.

Contour integration task

One subject (3274) was excluded from the analysis of contour integration because their performance never exceeded chance. There was no significant effect of dosing sequence or days elapsed since last exposure to an MDMA-like drug. Dosing condition alone did not predict threshold orientation jitter ($F_{1,10} = 0.409$, $p = 0.537$). However, when peak CEVs was added as a predictor, there was a significant main effect of CEVs ($F_{1,9} = 9.385$, $p = 0.014$) and a significant interaction with dosing condition ($F_{1,9} = 17.972$, $p = 0.022$). This relationship is depicted in **Figure 2.11**, where lower thresholds indicate worse performance. Greater CEVs predicted worse contour integration. In contrast, peak overall drug effect did not significantly predict threshold. Equivalent results were seen when simple accuracy was used as the dependent measure.

Object recognition task

Data were missing for one individual's MDA session due to a computer error. There was no significant effect of dosing sequence on object recognition accuracy. A linear mixed-effects model where accuracy was predicted by cue type and dosing condition resulted in main effects of cue type ($F_{2,52} = 6.035$, $p = 0.004$) and condition ($F_{1,52} = 6.058$, $p = 0.017$), but no interaction. Accuracy on trials with true cues was estimated to be 7.2% higher than in either no or false cue trials. Accuracy on MDA was estimated to be 4.9% lower than on placebo (**Figure 2.12**). Adding degradation level to the model revealed significant effects of degradation level ($F_{1,46} = 4.334$, $p = 0.043$) and an interaction of dosing condition and degradation level ($F_{1,46} = 6.693$, $p = 0.013$), indicating that participants on MDA were more impaired by image degradation.

Examining only the accurate trials, I constructed a mixed-effects model predicting the degradation level at which stimuli were correctly identified. This also revealed significant main effects of dosing condition ($F_{1,52} = 6.3148$, $p = 0.0151$) and cue type ($F_{2,52} = 43.3203$, $p < .0001$) on degradation level of correct identification, though there was again no significant interaction.

I then collapsed across cue types and tested for a relationship between performance and self-report visual change. I found significant main effects of CEVs ($F_{1,10} = 20.337$, $p = 0.001$) and condition ($F_{1,9} = 8.736$, $p = 0.016$), as well as a significant interaction term ($F_{1,9} = 11.499$, $p = 0.008$), in predicting accuracy. Increased CEVs reduced accuracy for MDA and placebo, 0.2% and 0.1%, respectively, for each percent increase in CEVs. This effect is significantly larger for MDA than placebo ($t=3.391$, $p = 0.008$). See **Figure 2.13** for a depiction of this relationship. This relationship appeared to be specific to visual effects rather than overall drug effects, as peak overall effects was not significant when added to the statistical model. Similarly, there was no significant effect of dosing sequence. Unlike accuracy, degradation level for correct trials was not significantly predicted by CEVs.

DISCUSSION

This study is the first, to my knowledge, to measure the perceptual effects of the hallucinogen MDA. I found that MDA produced a significant increase in closed-eye visuals (CEVs), with considerable individual variation. Alles [144], who first studied MDA in self-experiments, reported experiencing visual percepts of smoke rings. However, subsequent researchers have emphasized the unusually consistent social and emotional effects of MDA rather than the visual changes [145-147]. Given that drug-induced CEVs are more easily elicited than open-eye visual changes, one might speculate that MDA-induced extraversion decreases likelihood of closing eyes and experiencing visual percepts. Nonetheless, it seems likely that the visual effects of MDA are more subtle than those of hallucinogens such as mescaline and psilocybin, which often produce dramatic open-eye visual percepts [286, 453].

Magnitude of CEVs after MDA was associated with lower performance on the two measures of perceptual organization. In both cases, there was also a significant

interaction with dosing condition, suggesting that individuals who saw more intense CEVs both had poorer overall performance on these tasks and also had greater MDA-induced changes in perceptual performance. This finding is consistent with evidence linking hallucinations to decreased sensory fidelity and impaired perceptual organization [373, 387, 416]. Furthermore, acute effects of MDA on the contour integration task match acute effects previously reported for the NMDA antagonist hallucinogen ketamine [436]. While decreased perceptual performance in MDA sessions could be partly due to nonspecific drug effects, I was not able to find a significant relationship between overall self-report effects and impaired perceptual performance. Furthermore, the association of CEVs and uninebriated perceptual performance suggests those with poor perceptual organization may be more likely to experience hallucinations. My study is not able to specify the underlying mechanism of this potential relationship. Further research will be needed to determine if this is the result of relatively low-level sensory fidelity changes (such as changes in gain control of thalamic or cortical neurons), perceptual organization effects, or higher-level cognitive changes.

In addition to decreased perceptual ability, hallucinations have also been linked to abnormal excitation in a number of disorders, such as migraine and epilepsy [309, 310, 314]. Although increased occipital cortex excitation is predicted by Ermentrout and Cowan's model of geometric hallucinations [87], it has never been studied during acute hallucinogen effects to my knowledge. I was not able to find evidence in support of increased occipital cortex excitation using the tilt illusion in planned analyses. However, when I examined only the tilt illusion results from the first session, my exploratory analysis revealed possible evidence of residual effects of MDMA-like drugs in the task.

Residual effects of MDMA-like drugs in the tilt illusion were not unexpected. There have been previous reports of residual effects of MDMA in the closely related tilt aftereffect [371, 372] as well as evidence of lasting changes in occipital cortex excitability measured with TMS or fMRI [454, 455]. In addition, some MDMA users report persisting visual percepts, as documented in Chapter 1 and in case reports [220, 221]. Geometric visual percepts were reported by 24.2% of respondents in Chapter 1 (excluding times when they had used a drug within three days). Alternatively, the apparent sequence effect could be explained by between-subject differences in this small study. If confirmed, the possibly increased cortical excitability suggested by my exploratory tilt illusion results would provide a plausible mechanism for the geometric pattern hallucinations sometimes reported by such individuals.

A third factor that might contribute to the mechanism of drug-induced hallucinations is cognitive changes. Hallucinations have been hypothesized to be produced by increased influence of top-down factors on perception. I found that participants made effective use of true cues during their MDA session and, if anything, performance in trials with false or no cues may have been differentially impaired. However, I was not able to confirm a statistical interaction between cue type and dosing condition in the object recognition task. One limitation to the task is that it did not allow me to cleanly distinguish criterion shifts from changes in sensitivity, which may have decreased my ability to detect drug effects. Thus, I cannot confirm or deny the role of strengthened top-down factors in MDA-induced hallucinations.

Furthermore, the object recognition task only manipulated one kind of top-down influence, with cues essentially functioning as semantic primes. Each cue would be expected to activate high-level representations of the cued object, but —because participants were told the cue had 50% accuracy— would not create a strong expectation that the cue was correct. This chance cue accuracy was selected to minimize response biases. Nonetheless, the task did not allow me to isolate the type of top-down attentional changes that are normally measured in, for example, the Posner cuing task [456]. In that task, top-down changes are typically assessed using 65% to 80% accurate spatial cue that is compared to a 50% accurate cue. Tasks like this that manipulate the likelihood of different stimuli might also be useful in studying drug-induced hallucinations.

There were several limitations to my tests of hallucination mechanisms that were imposed by the overall study design. To begin with, my participants were all experienced users of MDMA and hallucinogens. This was an ethical consideration intended to minimize risk of idiosyncratic reaction and facilitate informed consent. Another limitation was that dosing sessions were on consecutive days in order to maximize measurement of the pharmacokinetics of a presumably long-half-life drug while minimizing blood samples from participants. Although such trade-offs are a necessary part of clinical research with psychoactives, possible residual drug effects may have limited my ability to detect the acute effects of MDA. Thus, further research with MDA will be needed in order to confirm and extend my findings.

One potentially promising approach would be to use noise masking and signal detection theory to examine mechanisms of hallucinogen-induced visual changes [457-460]. This would allow us to mathematically separate different sources of altered efficiency, such as increased internal noise or inefficient use of available information. Additionally, repeating these tasks with other serotonergic hallucinogens, such as LSD and psilocybin, might allow a better understanding of the relationships between neuropharmacology of hallucinogens and their complex phenomenology.

In conclusion, I conducted the first study to my knowledge of the perceptual effects of the hallucinogen MDA, confirming that the drug does induce CEVs in at least some individuals. Magnitude of CEVs after MDA was associated with lower performance on measures of contour integration and object recognition, supporting a hypothesized link between hallucinations and impairments in sensory and perceptual processing. In contrast, I was unable to provide strong evidence for changes in efficacy of top-down influences on perception or acutely increased occipital cortex contributions.

Table 2.1: Participant demographics for MDA study.

Participant Code	Age	Gender	Race	Ethnicity	Years of Education Completed
1843	39	Male	Not Hispanic or Latino	White	18
3057	43	Female	Not Hispanic or Latino	White	14
3150	21	Male	Not Hispanic or Latino	White	13
3158	21	Male	Not Hispanic or Latino	White	13
3179	32	Male	Not Hispanic or Latino	White	17
3261	23	Male	Not Hispanic or Latino	White	14
3274	26	Male	Not Hispanic or Latino	White	18
3304	29	Male	Not Hispanic or Latino	White	18
3496	20	Male	Hispanic or Latino	White	13
3512	22	Male	Not Hispanic or Latino	White	13
3569	20	Male	Not Hispanic or Latino	White	13
3570	38	Male	Hispanic or Latino	Black or African American	14

Figure 2.1: Illustration of the tilt illusion. Central gratings are both oriented vertically, but appear to many observers to be tilted in the opposite direction of surrounding gratings (which are tilted 10° from vertical).

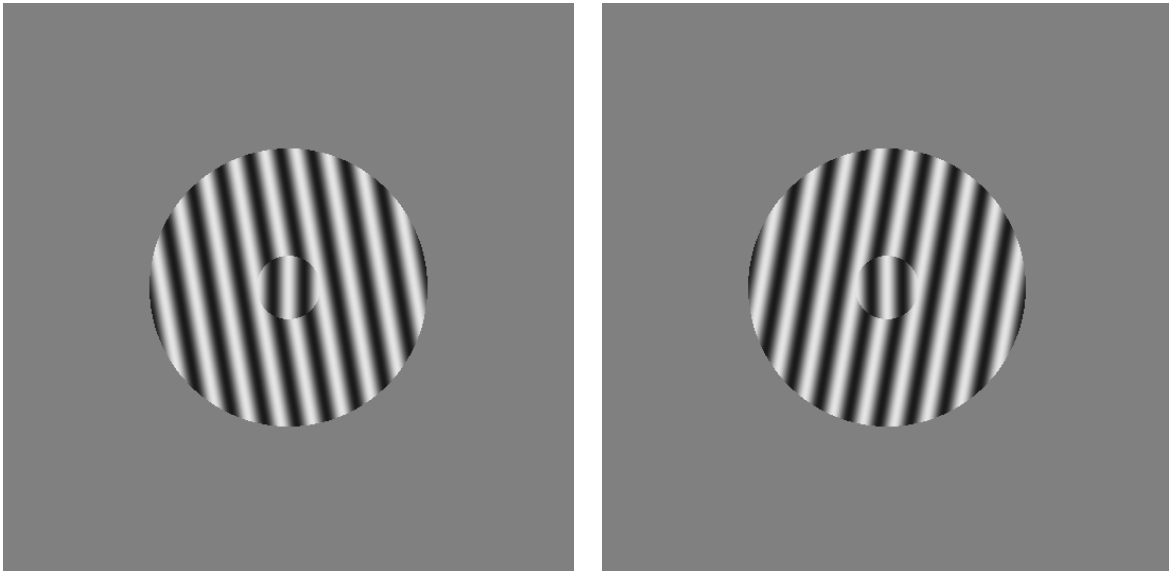
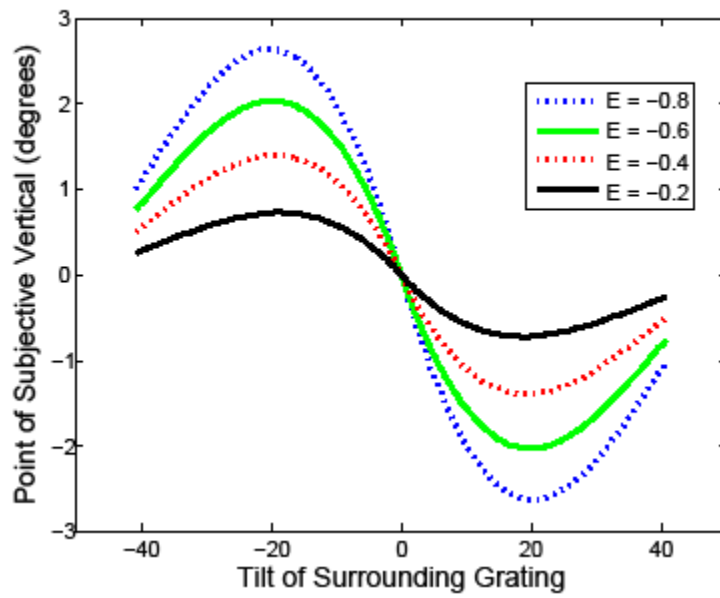


Figure 2.2: Influence of lateral interactions on Tilt Illusion in a Wilson-Cowan mean field model of the cortex



Increasing the strength of lateral interactions (E) increases the magnitude of the Tilt Illusion in Yang's Wilson-Cowan equation model of the cortex [2].

Figure 2.3: Sample contour integration stimuli showing egg-shaped contours in an easily discriminable no jitter condition (left top) and a more difficult condition in which contour elements have been randomly jittered by 11-12° (left bottom). On the right, the same stimuli are shown without the randomly oriented background Gabor patches, illustrating how these ‘noise’ elements impair contour recognition.

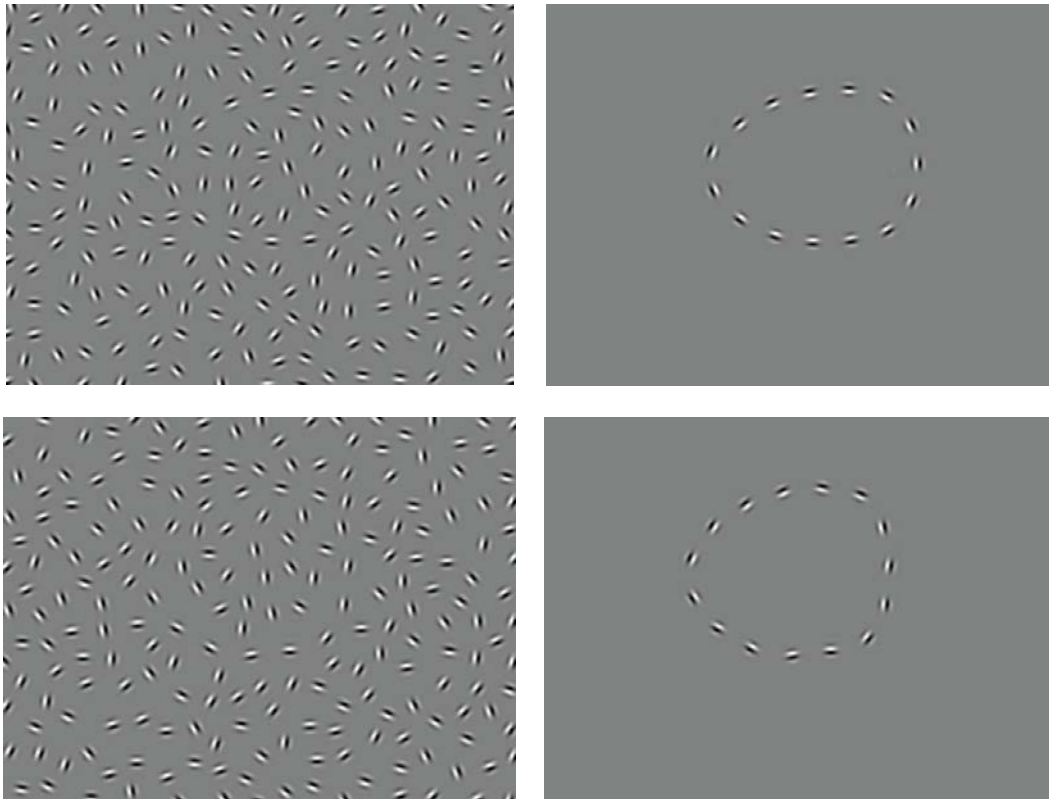


Figure 2.4: Sample object image at four levels of degradation

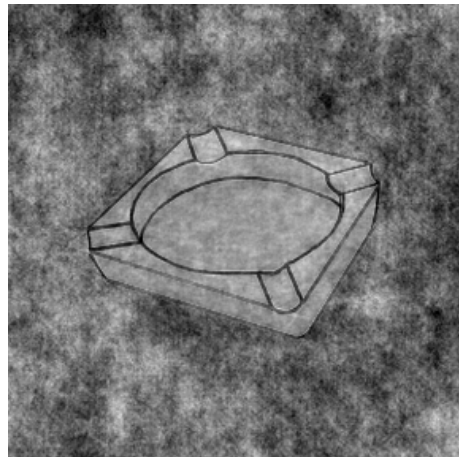
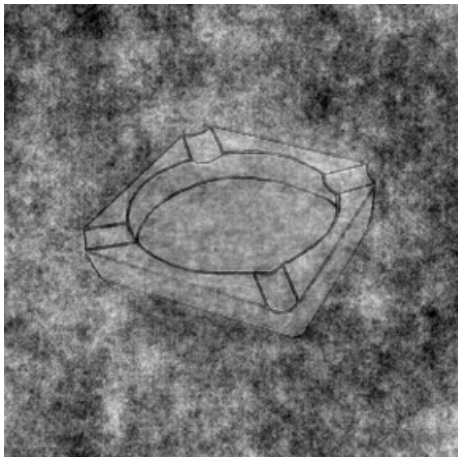
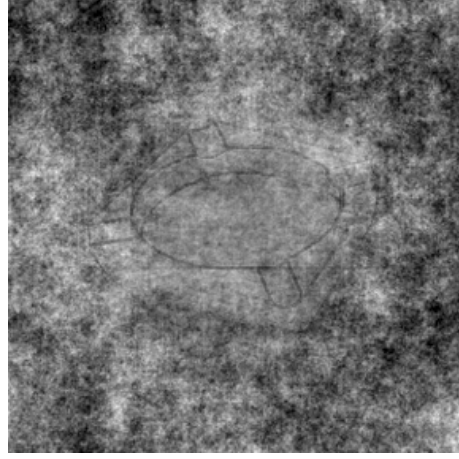
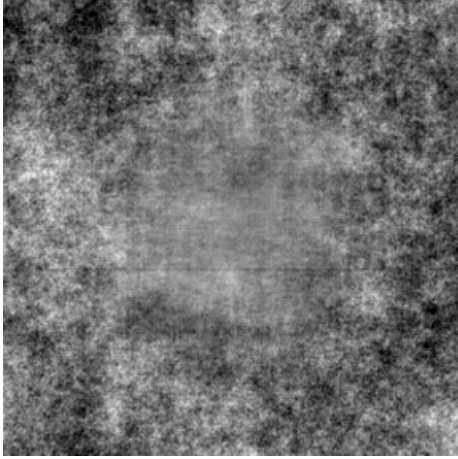


Figure 2.5: Time course of self-report overall drug effects

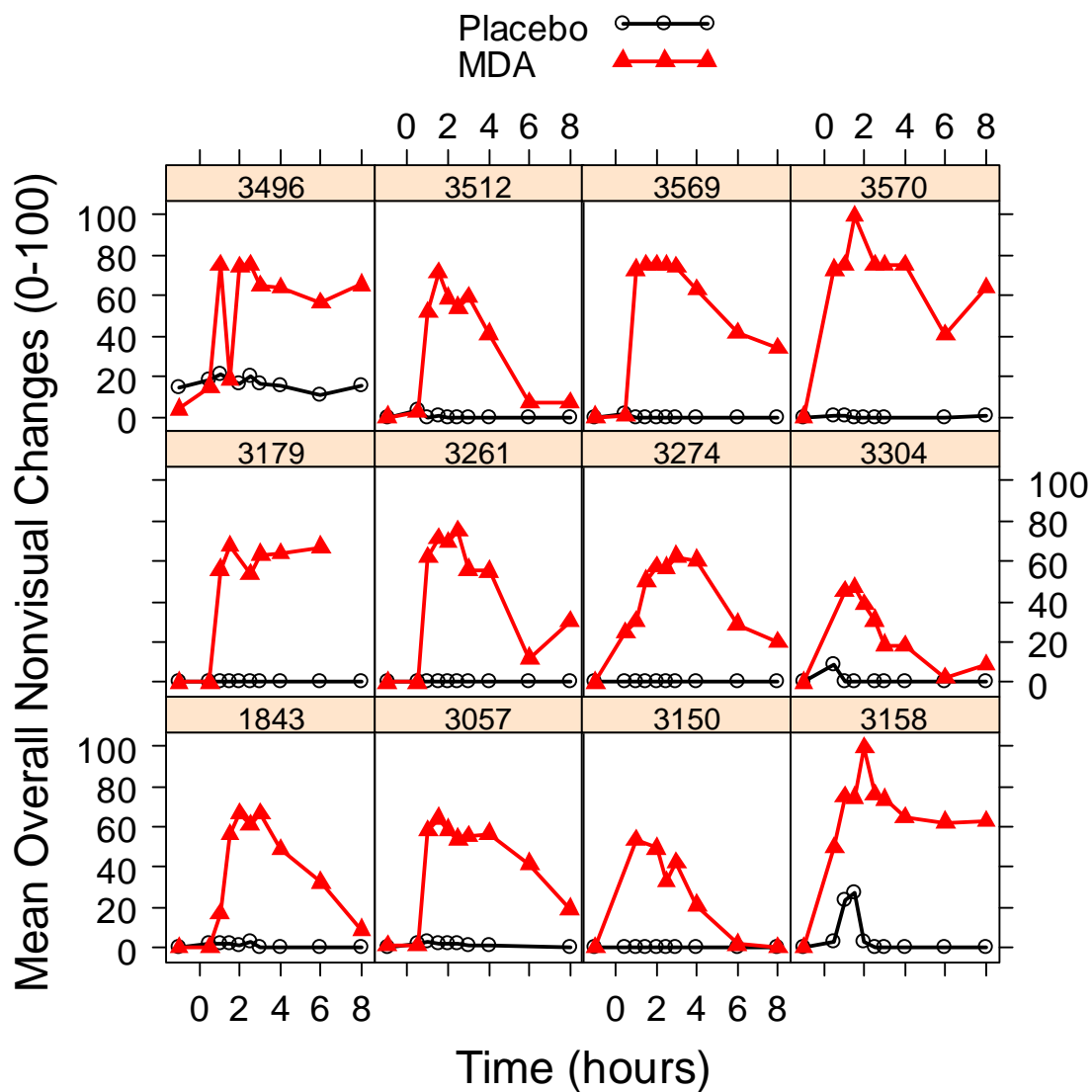


Figure 2.6: Time course of self-report closed-eye visuals

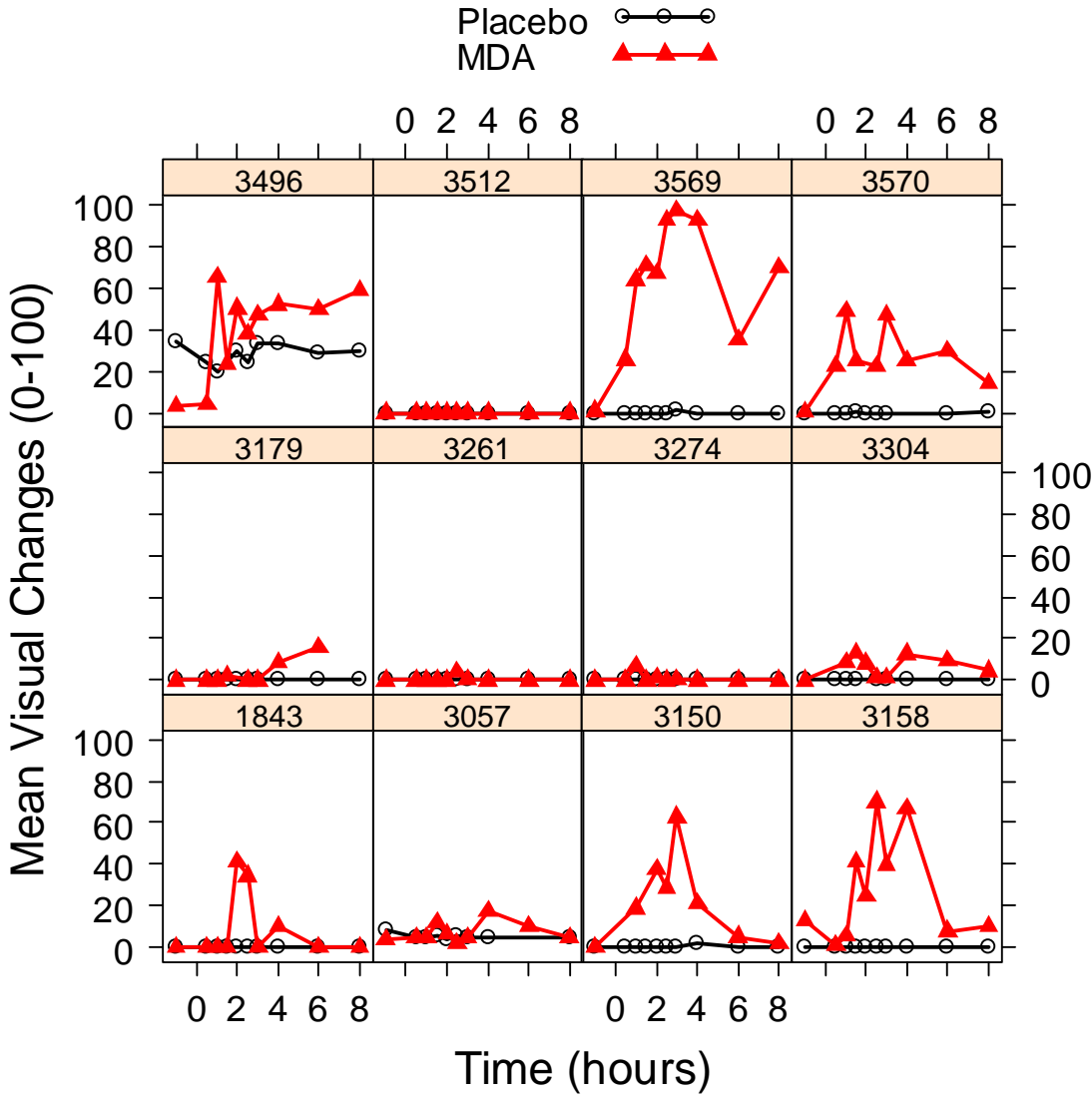


Figure 2.7: Group means for categories of drug effects after MDA, with standard error of the mean error bars omitted from the lower plot.

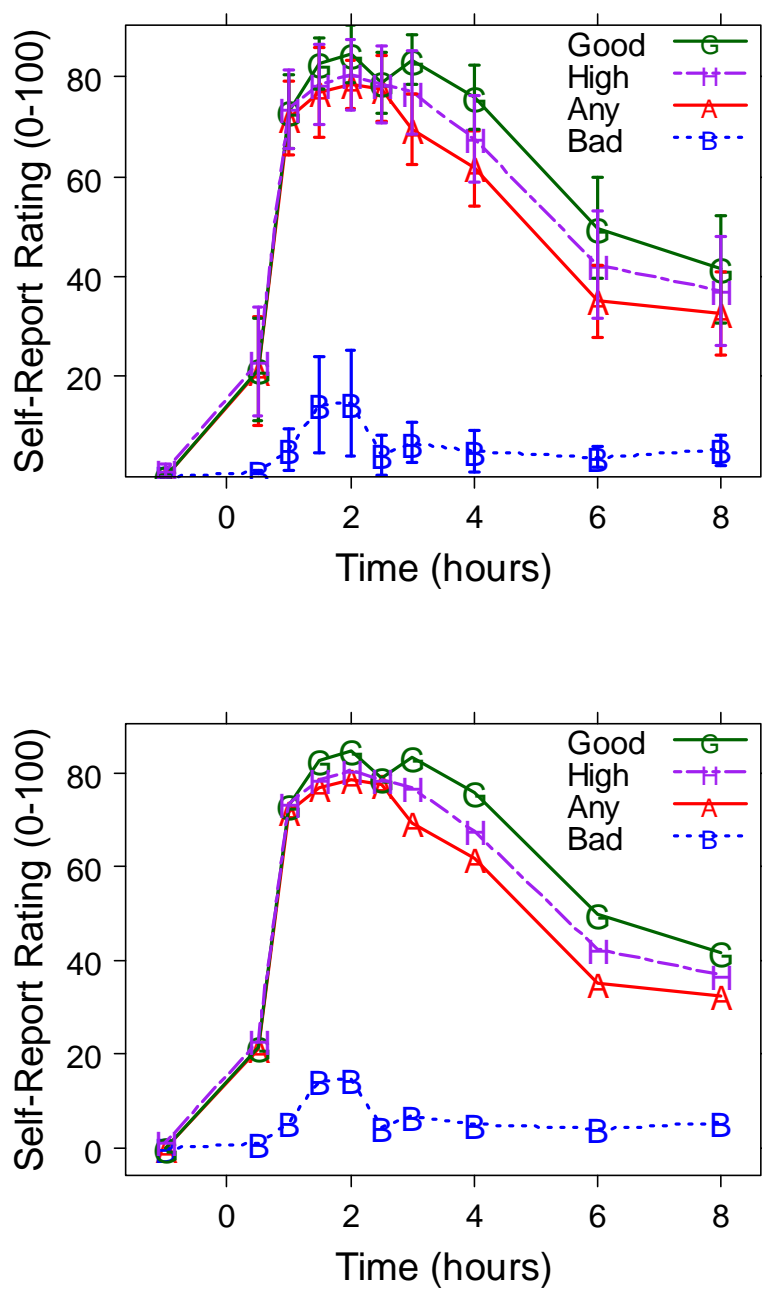


Figure 2.8: Group means for categories of closed eye visuals effects after MDA, with standard error of the mean error bars omitted from the lower plot.

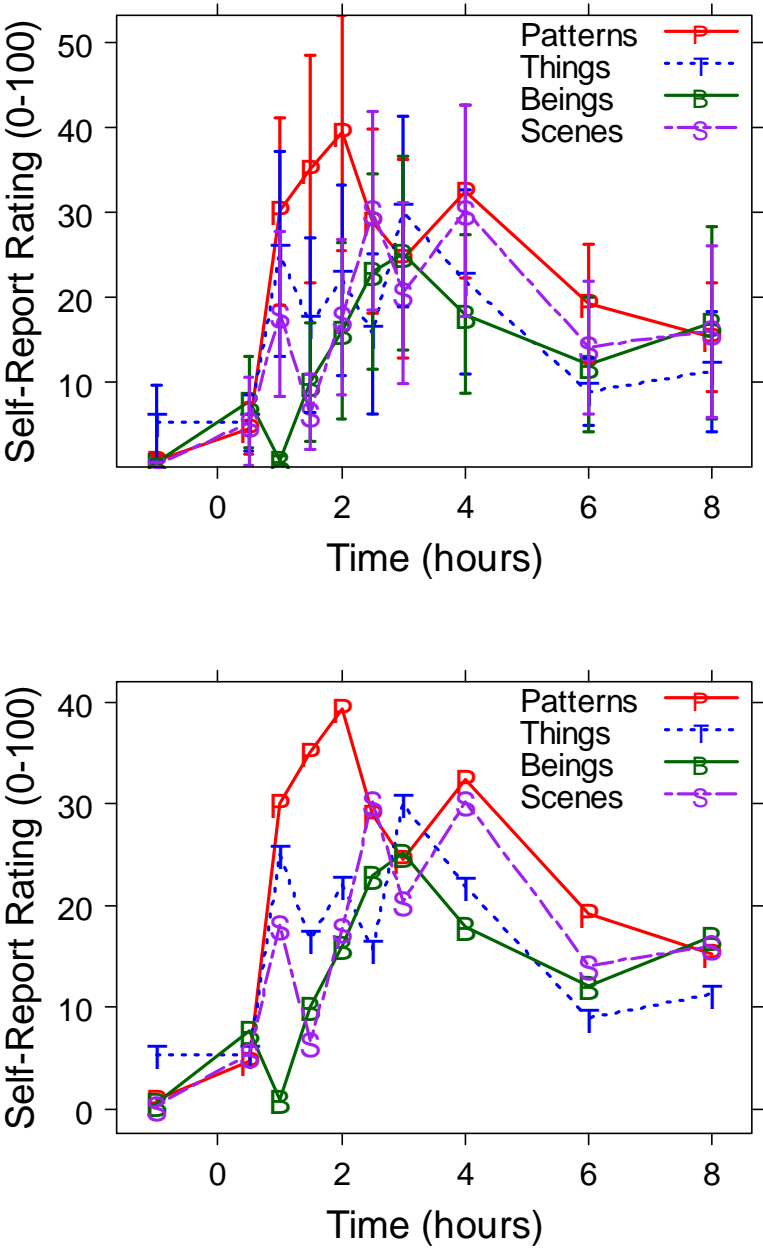


Figure 2.9: Tilt illusion performance for individuals, with black indicating placebo and red indicating MDA

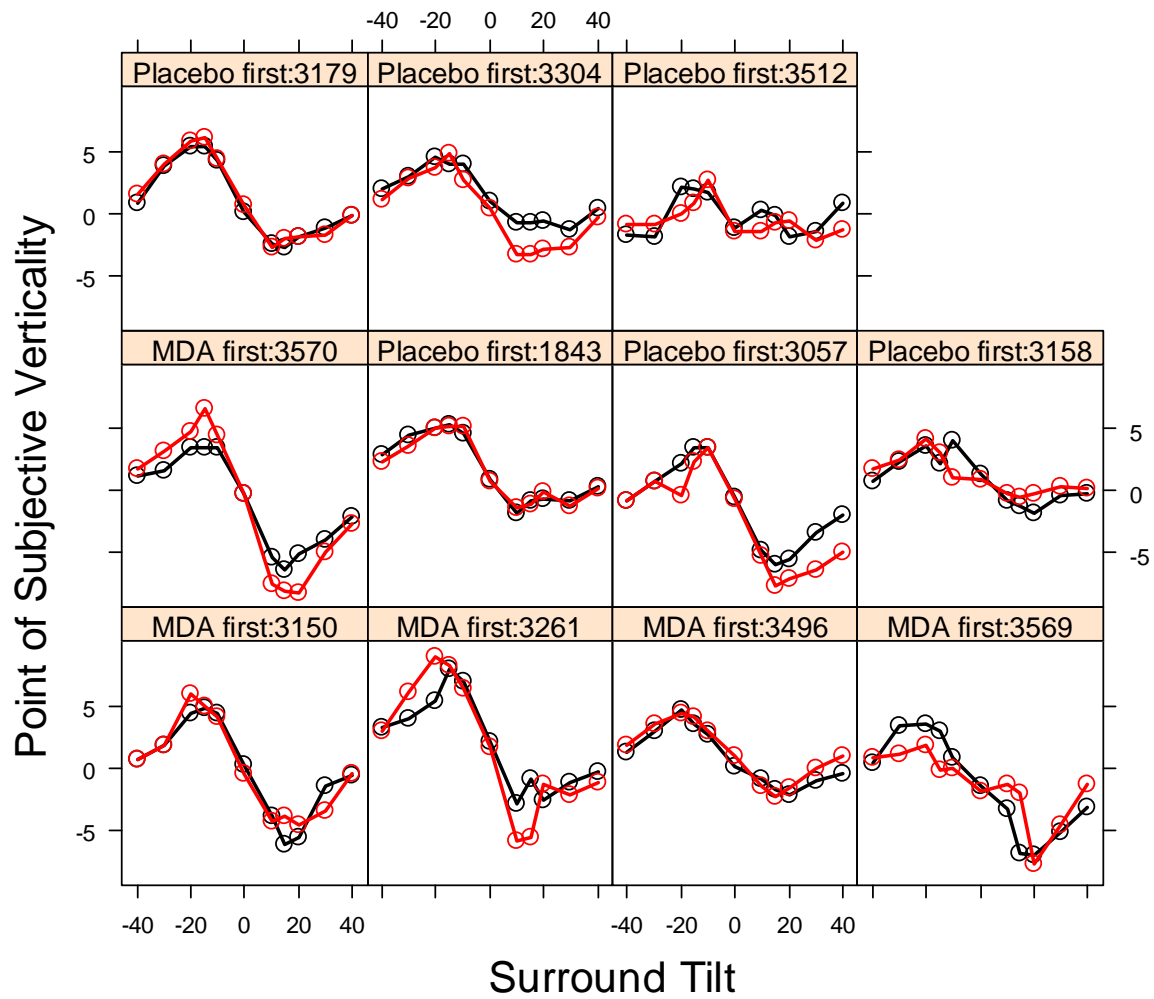


Figure 2.10: Tilt illusion is larger for those who received MDA first

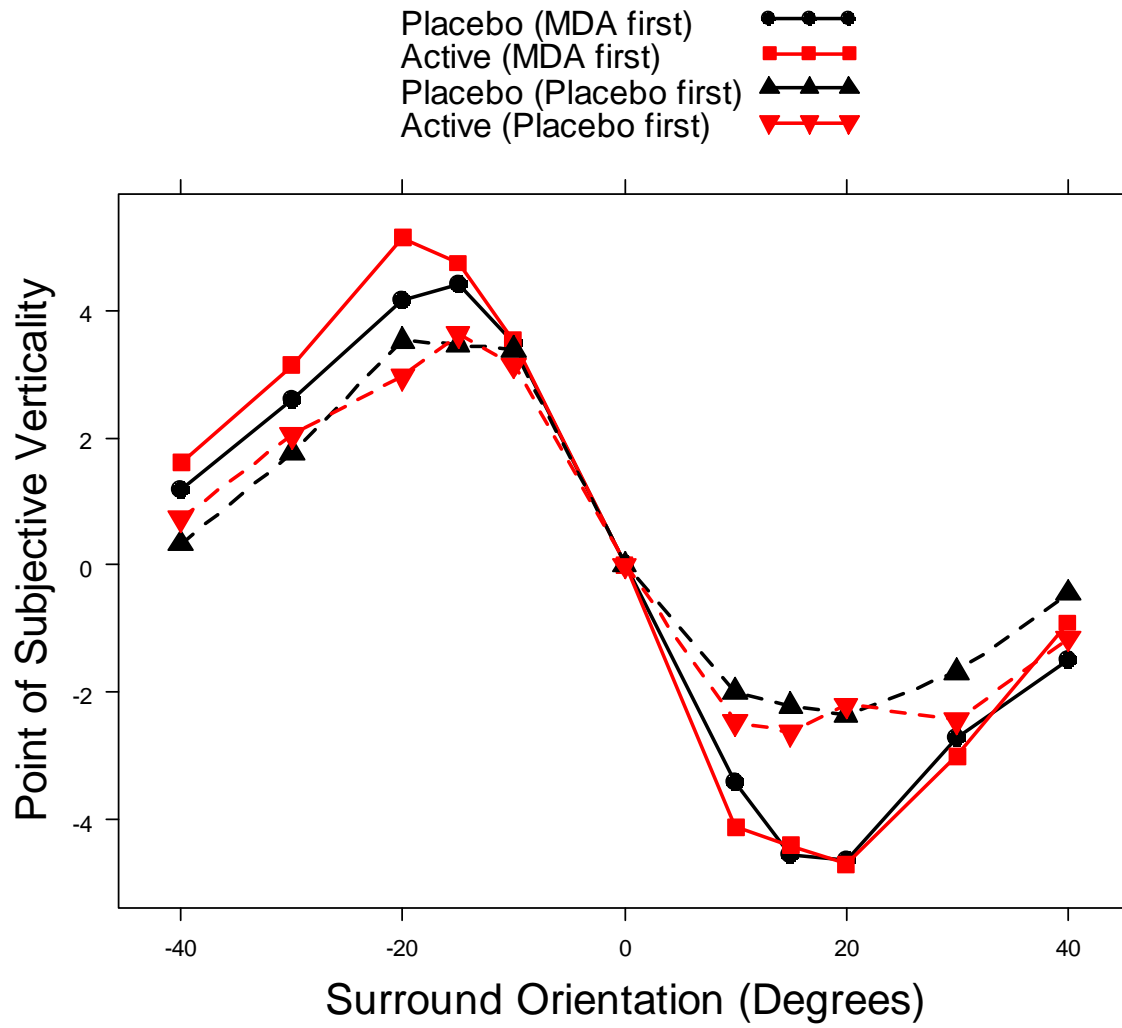


Figure 2.11: Contour integration showed an interaction of dosing condition and closed-eye visuals

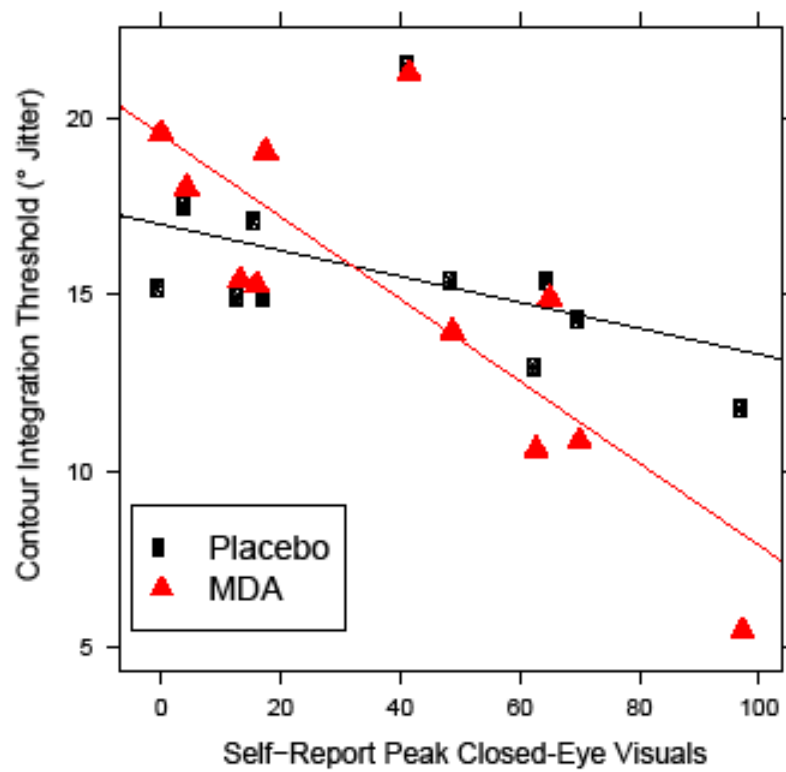
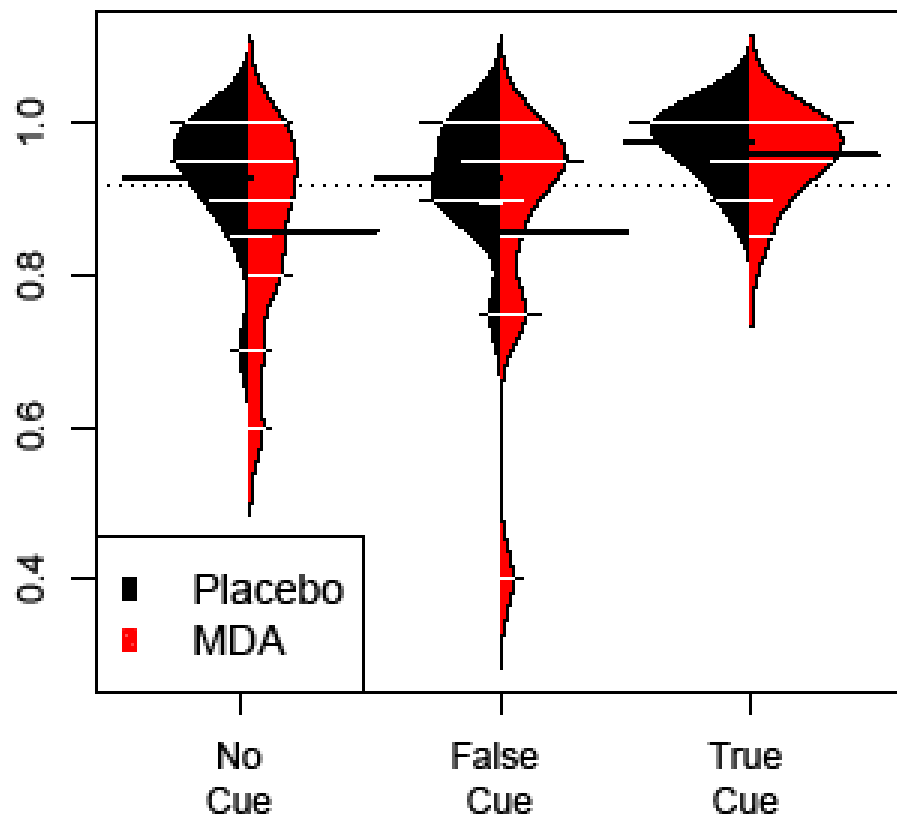
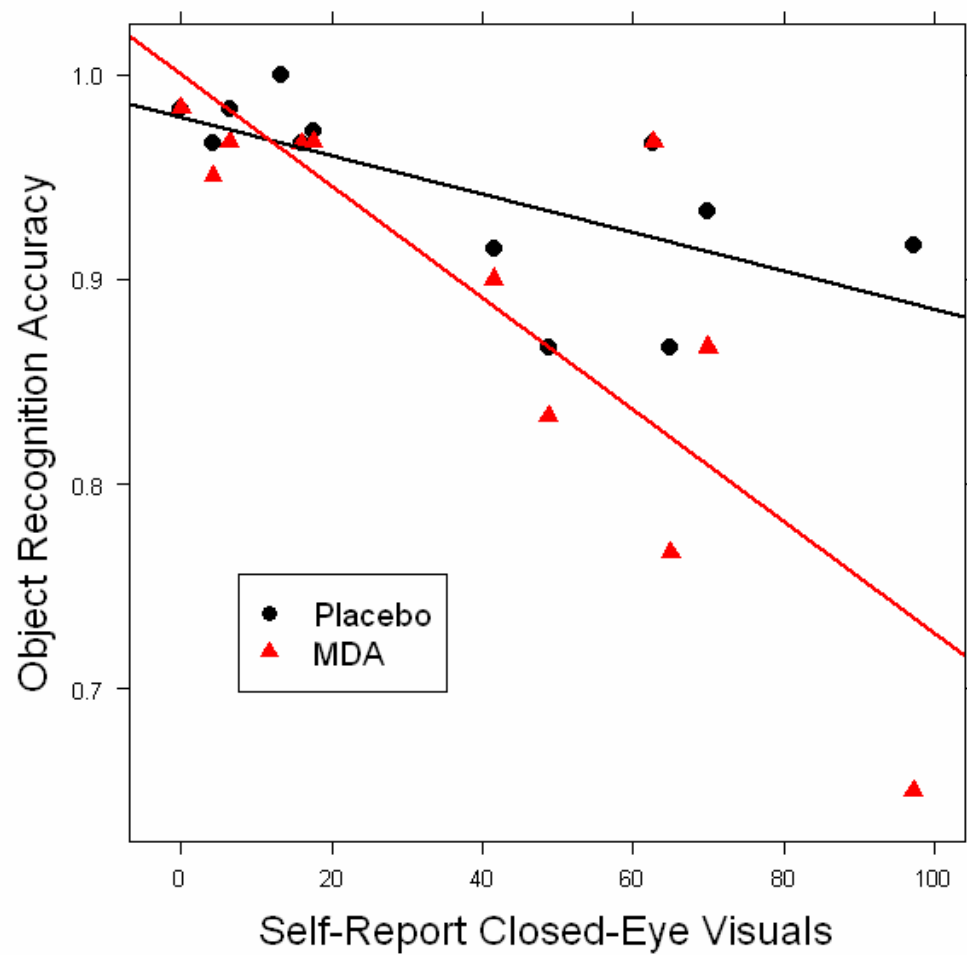


Figure 2.12: Beanplot showing object recognition accuracies for cue types in both conditions.



Contours indicate probability distribution functions with placebo in black and MDA in red. White lines are horizontal histograms indicating distribution of accuracies. Solid black lines indicate means for each condition and cue type. Dotted line indicates mean for entire sample.

Figure 2.13: Scatterplot object recognition accuracies showing interaction of dosing condition and self-report closed-eye visuals.



CHAPTER 3: Attentional Effects of Serotonergic Drugs

In the previous chapter, I used what could be described as “cold” measures of drug effects. However, 5-HT is closely associated with “hot” affective processing. The serotonergic system appears important for evaluation of social stimuli and may modulate amygdala sensitivity to threat-related stimuli. Hallucinogens and related serotonergic drugs vary in their ability to release 5-HT, but no studies have measured how these drugs affect attentional biases for emotional stimuli. In this chapter, I describe two double-blind placebo-controlled experiments on the effects of the serotonergic drugs 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) on attention to emotional stimuli. Using a dot-probe task (described below), I found preliminary evidence that MDA and MDMA may modify processing of threat-related stimuli. These effects appear unrelated to state anxiety. In contrast, I did not detect significant effects of the selective serotonin reuptake inhibitor (SSRI) citalopram.

BACKGROUND

I used the dot probe task to implicitly measure attentional bias for emotional stimuli. I begin by describing the task and reviewing past studies that have used it to assess processing of threat-related stimuli. Then, I describe the rationale for studies using the dot-probe paradigm to measure the effects of serotonergic manipulations on attention to emotional faces. I then review the literature on threat vigilance and attention and describe the apparently specific role of serotonin in altering processing of threats that are associated with amygdala function. Finally, I describe the predicted effects of different serotonergic manipulations on the task.

Dot probe task as a measure of attentional bias

In the dot probe task, participants fixate on a central location and make easy discriminations about dot pairs that appear randomly in one or two (peripheral) locations. Participants make speeded judgements (using a key press) of the orientation of the dot pairs, which are either vertical (like a colon character) or horizontal (like two period characters) and are highly discriminable. In order to implicitly assess attention to emotional stimuli, researchers briefly display task-irrelevant stimuli in the two possible probe locations shortly before the dot pair is shown. If one of the stimuli draws the attention of participants, it is predicted to alter response time to the dot pair probes.

Thus, the dot probe task measures vigilance for emotional stimuli by measuring altered response times for probes that appear in spatial locations previously occupied by task-irrelevant emotional stimuli [456, 461-465]. Shorter response latencies when probes replace emotional stimuli are often hypothesized to occur because the stimuli drew attention to the location, facilitating subsequent detection of the probe. In addition, difficulty disengaging from that location may lead to longer response times for probes in other locations. Earlier research did not distinguish between these two factors (preferential engagement to a salient location versus difficulty disengaging from that location) and the most common measurement of attentional bias in the dot probe

literature does not distinguish between these possibilities. More recently, however, comparisons of response latencies to neutral stimuli suggest that difficulty disengaging attention is usually the more significant factor [464, 466]. Evidence for both processes has been seen in studies using visual search and Posner cuing paradigms (reviewed in [467]).

A rich literature of past studies provides ample reasons to use this paradigm. The dot probe task has shown differential processing of threat-related stimuli in a variety of populations, including people with high state [468] or high trait anxiety [469], generalized anxiety disorder [470], and social phobia [471]. Specifically, studies using dot probe paradigms find that individuals with high anxiety are faster to respond to probes that replace threatening stimuli than probes that replace neutral stimuli compared with low-anxiety controls, suggesting increased attention to the location of the threat stimuli [472-474]. (Dot probe experiments are summarized in more detail in a subsequent section). The involvement of the amygdala in processing of threat-related stimuli during the dot-probe task has been demonstrated by two fMRI studies [475, 476]. Pharmacological studies indicate that several variations of the dot probe task are sensitive to acute and subchronic serotonergic manipulations. Browning et al. [477] found that a single oral dose of 20 mg of the SSRI citalopram quickened responses to stimuli that replaced positively valenced words in a dot probe task that used word stimuli. Murphy et al. [478] administered 20 mg citalopram per day for seven days and found that attentional bias to fearful faces was reduced compared to placebo. No effects on this task were seen using happy face stimuli nor was there any effect of giving the selective norepinephrine reuptake inhibitor reboxetine (8 mg/d). Therefore, using the dot probe task allows comparisons of results with a variety of clinical populations and pharmacological manipulations, including serotonergic ones.

In addition, the task may provide different information than the more widely used emotional Stroop task. Attentional biases in the Stroop and dot probe are not correlated [472, 479, 480], probably because these tasks are measuring different processes (i.e., response inhibition in the case of the Stroop task and attentional allocation in the dot probe task) [467].

Threats, anxiety, and psychopathology

Findings using the dot-probe task are consistent with numerous studies reporting that anxious individuals have a tendency to allocate attention toward threat-related stimuli over neutral or positive stimuli. The link between anxiety and attentional biases for threat-related stimuli has been shown using a variety of attentional paradigms. Variations of the Posner cuing task that employ threat-related spatial cues provide evidence that individuals with high anxiety have increased difficulty disengaging attention from locations where threat stimuli have appeared [474, 481, 482] as well as potentially increased vigilance for threats [465, 473, 483, 484]. Visual search tasks in which participants detect a target stimulus embedded in a matrix of distracting stimuli allow measurement of detection of threat-related targets in a matrix of emotionally neutral distracters as well as neutral targets in a matrix of emotional distracters [485, 486]. Alterations in visual search have been reported to occur in individuals with generalized

anxiety disorder [486] and arachnophobia [487, 488]. Individuals with anxiety disorders are reportedly more likely to interpret ambiguous stimuli as threatening [489-491]. Such biases to negatively interpret emotionally ambiguous stimuli have been seen in studies using facial expressions [492], verbal stimuli (e.g., homophonic words and phrases with threat and non-threat meanings, such as “patient” (hospital versus calm) or “the artist drew the gun”) [493, 494], and complex social vignettes [495]. A meta-analysis by Bar-Haim et al. [496] found a modest effect size of $d = 0.45$ for bias toward threat-related stimuli when 172 studies using different stimuli, populations, and paradigms were analyzed. Some degree of vigilance for potential threats is almost certainly a survival-enhancing, innate mechanism [485, 497]. However, excessive concern for potential threats can become dysfunctional. Indeed, exaggerated threat vigilance is characteristic of anxiety disorders such as posttraumatic stress disorder [498].

The relationship between anxiety and attention is of theoretical interest because it may shed light on ways to improve prevention and treatment of mood and anxiety disorders. Many have suggested that exaggerated processing of threat-related stimuli may contribute to the development and maintenance of clinical states of anxiety [499-501]. Recent cognitive theories of antidepressant mechanisms suggest that these drugs might work in part by rapidly shifting attentional biases from negatively valenced to positively valenced information and that the resulting positive bias eventually leads to decreases in psychiatric symptoms [502]. Consistent with this possibility, MacLeod et al. [503] reported differential anxiety in participants who had been trained in a dot probe task to either attend towards or away from threat-related stimuli. This indicates that attention to certain stimuli may give rise to anxiety in at least some cases. Nonetheless, the causal relationship(s) between anxiety and attention to threat-related stimuli has not been fully resolved [467, 503, 504].

Neurocognitive mechanisms of anxiety

Neuroimaging studies provide evidence that functional circuits, including the amygdala and prefrontal cortex, rapidly encode the presence of threat-related stimuli [84-86]. Rapid amygdala response to threat-related stimuli has been hypothesized to be facilitated by subcortical tecto-pulvinar pathways that provide coarse low spatial frequency information to the amygdala before slower cortical processing of higher spatial frequencies can occur [505]. Compared to the response to emotionally neutral stimuli, the blood oxygen level dependent (BOLD) signal that is commonly used in fMRI studies is greater in the amygdala after a variety of threat-related stimuli [506, 507]. This amygdala responsiveness is increased in depression [508-511]. However, the sensitivity of the amygdala to threat-related stimuli cannot be taken as evidence that it functions as a “threat detector”. Instead, it may play some more general role in emotional evaluation of environmental stimuli [512-514]. Similarly, despite a robust literature showing amygdala activation to emotional stimuli presented outside of conscious awareness (e.g., [515-517]), perceptual load influences the degree of amygdala processing of unattended stimuli [518], consistent with the attentional research carried out by Lavie and colleagues [519]. Bishop [520] has suggested that increased amygdala activity associated with anxiety may be partly due to diminished recruitment of top-down attentional mechanisms

to support appropriate processing of task-relevant stimuli and/or to inhibit the further processing of threat-related distracters.

Serotonergic influences on emotion, anxiety, and threat processing

The literature supporting an important relationship between serotonin and anxiety is large enough to defy ready summary. From a neuroanatomical perspective, the amygdala has a relatively high density of SERT [521]. Interestingly, while serotonin probably acts through volume transmission throughout much of the brain, Freedman and Li [35] reported a pattern of distribution of immunoreactivity for serotonin and SERT in the extended amygdala of macaque monkeys that was more consistent with a classical neurotransmitter pattern. Thus, serotonin appears to be modulating the amygdala with high temporal and spatial specificity.

Evidence that the serotonergic system significantly modulates amygdala activity in humans comes from studies combining genetic and functional imaging measures. Reactivity of the amygdala to emotional stimuli has been reported to be modulated by genotype of the promoter region of the serotonin transporter (5-HTTLPR) in depressed [522] and healthy individuals [523-526]. Two studies [527, 528] but not a large recent study [529] reported associations between 5-HTTLPR genotype and baseline perfusion in the amygdala and the medial temporal lobe using perfusion imaging. Consistent with theories that frontal cortex regulation of the amygdala is important, Fisher and colleagues [530] recently reported that greater mPFC 5-HT_{2A}R density was associated with reduced threat-related right amygdala reactivity, with 25-37% of the variability in amygdala reactivity being explained by density of 5-HT_{2A}R in mPFC. Fisher et al. [531] also reported that variation in dorsal raphe 5-HT_{1A}R binding potential explained 30–44% of the variability in bilateral amygdala reactivity during an emotional faces–matching protocol in a study that combined [¹¹C]WAY100635 positron emission tomography and fMRI measures. Dorsal raphe 5-HT_{1A}R are autoreceptors and play a negative feedback role, reducing subsequent serotonergic firing after they are stimulated. Thus, there is *in vivo* evidence that amygdala reactivity is under serotonergic control directly from raphe nuclei and by indirect modulation of frontal cortex.

Manipulating 5-HT levels in humans

5-HT can be acutely altered in humans in three main ways: (1) acute tryptophan depletion, (2) acute enhancement with single administration of a SSRI or dietary 5-HT precursor; and (3) acute enhancement with a 5-HT–releasing agent. These serotonergic manipulations generally do not have broad cognitive effects and seem to have relatively focused effects on measures relevant to anxiety, punishment, and emotional and social factors.

5-HT can be acutely decreased in humans using acute tryptophan depletion (ATD). In this procedure, a tryptophan-free amino acid drink is given, causing a depletion of central 5-HT over the course of several hours [532]. General effects of ATD on psychomotor processing, declarative memory, working memory, executive functions and attention were recently reviewed by Mendelsohn, Riedel, and Sambeth [533]. Overall, ATD does

not appear to alter most of these processes. The most reliable effect of ATD was worsened consolidation of episodic memory for verbal information, a difficult task that is often sensitive to nonspecific impairments from factors like distraction due to somatic symptoms.

In addition, ATD causes affective changes and alterations in emotional processing. Individuals with high risk for depression may experience decreased mood or depressive symptoms, but there are no mood changes and only subtle changes in healthy volunteers. Nonetheless, there appears to be subtle biases in processing of emotional stimuli in healthy volunteers. For example, Harmer et al. [534] reported decreasing 5-HT by ATD significantly decreased recognition of fearful facial expressions in female, though not male, volunteers without altering recognition of other basic emotions or changing self-report mood or anxiety. Fearful faces are often interpreted as a social indicator of a potential threat. Thus, a selective change in processing of these expressions is frequently interpreted as decreased threat vigilance, consistent with ATD impairing a threat-sensitive system that is modulated by serotonin.

Acute increases in 5-HT have been produced with single administration of a SSRI or dietary 5-HT precursor. Attenburrow et al. [535] administered an 80% tryptophan powder to healthy females and found improved recognition of fear and happiness compared to placebo, reminiscent of a study by Harmer and colleagues on the effects of acute SSRI administration [536]. Again, these changes appear consistent with serotonergic manipulations altering a threat-sensitive system.

Extracellular 5-HT can also be increased using a pharmacological serotonin releaser. The most widely studied of these is fenfluramine. Most studies administering fenfluramine to humans have used resulting hormone changes as an index of serotonergic tone [537-543]. Few studies have measured attention or other aspects of cognitive functioning [544]. Interestingly, one study administering high doses reported hallucinogen-like symptoms [545] which could be interpreted as the high extracellular 5-HT concentrations altering the balance of activity at 5-HT_{2A}R compared to other receptors.

MDA and MDMA are also pharmacological 5-HT releasers. MDA and MDMA robustly induce a positive emotional state that is attenuated or blocked by pre-treatment with an SSRI in humans [171, 173, 174], suggesting an important (if poorly understood) role for 5-HT in the effects of these drugs. As discussed in the Introduction, I hypothesize that large increases in extracellular 5-HT may decrease the sensitivity and signal-to-noise ratio of a phasic threat-sensitive serotonergic signal, making it difficult for the individual to experience the normal emotional saliency of potential threats. While both MDA and MDMA induce 5-HT release, MDA has greater 5-HT_{2A}R agonist effects, suggesting that MDA will also have classical hallucinogen effects such as slowed response and possibly impaired attention [186-189].

More general relationships of mood and attention

In contrast to the robust literature on anxiety and attention, relatively few studies have investigated the attentional effects of positive affect. The broaden-and-build theory of

positive affect describes positive affect as broadening the scope of attention and widening the array of thoughts and actions that come to mind in a given situation [546]. According to this framework, positive affect stimulates cognitive processing that is top-down, integrative, and global in focus. Similarly, the affect-as-information hypothesis [547] associates positive affect with a broadened scope of processing. Both theories would seem to predict that broadened attention would impair tasks that required focused attention and exclusion of distracter stimuli. However, attempts to link affect and cognitive measures of attention and executive function have generally yielded inconsistent results, with a possible tendency for positive affect to weaken executive function [548-552]. Most of these studies have used emotionally neutral stimuli and it remains an open question if emotional stimuli might reveal more robust effects of mood on attention. Tamir and Robinson [553] reported an association of positive affect with attentional bias for positive versus neutral or negative verbal stimuli. In that study, daily experiences of positive affect influenced orienting to rewarding (but not neutral) stimuli. Thus, euphoria induced by a drug might nonspecifically impair selective attention or lead participants to preferentially attend to positive stimuli.

Hypotheses. I hypothesized that both drugs, by increasing extracellular 5-HT in a manner independent from serotonergic firing, would decrease the attention-modulating effects of threat-related stimuli. In contrast, citalopram was predicted to either increase or not alter attention to threat-related stimuli because it was predicted to enhance a phasic threat-sensitive 5-HT signal. Furthermore, I hypothesized that MDA (having 5-HT_{2A}R-mediated hallucinogen effects) would slow and MDMA (lacking them) would speed responding in the dot probe task.

METHODS

Data are presented from two separate pharmacological studies, each involving administration of serotonergic drugs to twelve healthy volunteers with previous experience with illicit serotonergic drugs. Thus, a total of twenty-four volunteers participated in the studies described in this chapter.

General design for MDA study. As described in the previous chapter, this double-blind, placebo-controlled clinical study was carried out in a hospital setting. Extensive safety monitoring was carried out before and after, until drug effects resolved. Participants returned to the laboratory two weeks after discharge to ensure residual toxicity was not present.

Participants were twelve healthy individuals with self-report experience with either MDA alone or experience with both MDMA and a hallucinogen such as LSD. None had any DSM-IV drug dependence diagnoses (other than nicotine or caffeine). Participants demographics were given in Table 2.1 of the previous chapter. Comprehensive safety screening procedures included health & physical, self-report drug history, 12-lead EKG, liver panel, and blood chemistry. Participants were asked to practice effective contraception during the study. Pregnancy and drug toxicology tests were performed before drug administration.

Experimental drug administration occurred after a 2-hour fast to minimize individual variance in drug absorption. Lactose in a gelatin capsule was used for the placebo. MDA was administered in a dose of 98 mg/70 kg body weight in a gelatin capsule identical to the placebo. Drug and placebo dosing occurred on consecutive days.

General study design for MDMA-Citalopram experiment

This double-blind, placebo-controlled clinical study was carried out in a hospital setting. This study differed from the MDA study in that participants were required to have previously experienced hangover-like effects from MDMA one to three days after use. This is because one of the study goals was to study MDMA's hangover-like residual effects (using additional procedures that are beyond the scope of this dissertation). To study these residual effects, the experimental design included an approximately one-week long period of daily citalopram administration, with measures of acute citalopram effects obtained on the first day. As a result, it was not possible to fully balance the dosing sequence.

Participants were twelve healthy individuals with self-report experience with MDMA and report of hangover-like after effects. None had any DSM-IV drug dependence diagnoses (other than nicotine or caffeine). Participant demographics are listed in Table 3.1. Comprehensive safety screening procedures included health & physical, self-report drug history, 12-lead EKG, liver panel, and blood chemistry. Participants were required to practice effective contraception during the study. Pregnancy and drug toxicology tests were performed before drug administration.

Extensive safety monitoring was carried out before and after dosing, with participants remaining in the hospital until drug effects resolved. Participants returned two weeks after discharge to ensure residual toxicity was not present.

Experimental drug administration occurred after a two-hour fast to minimize individual variance in drug absorption. Lactose in a gelatin capsule was used for the placebo. MDMA was administered in a dose of 105 mg/70 kg body weight in a gelatin capsule identical to the placebo. This dose is equimolar to the MDA dose. Generic citalopram tablets were over-encapsulated and administered as a dose of 20 mg. Drug administration sessions were separated by at least a week.

Self-report anxiety measures. I used the 12-item self-report Brief Fear of Negative Evaluation (BFNE) questionnaire to measure social anxiety [554] and the State-Trait Anxiety Inventory - State (STAI-S) to measure general anxiety [555]. Measures were made before and 1.5 hours after drug administration.

Dot probe task. My version of the task was modeled after that of Murphy et al. [478] and further adjusted in pilot experiments. Emotional stimuli were pairs of images of the same individual showing the following combinations of emotional expression: fearful-neutral, happy-neutral, and neutral-neutral. Stimuli were modified from photographs of 30 individuals in the NIMSTIM set [556], with images presented on a gray background.

The task was programmed using E-Prime 1.X, using a 100 Hz vertical refresh rate. The task was performed two hours after drug administration.

Participants initiated each trial with a key press. A fixation cross appeared at the center of the screen 500 ms later. After 700 ms, a pair of faces was presented above and below the fixation cross. Faces were shown for 30 ms and were immediately replaced by a probe, which appeared in the location of one of the face stimuli. The probe consisted of a pair of vertically or horizontally oriented dots. Participants were required to indicate the dot orientation by pressing labeled keys on a keyboard with their left and right index fingers. The dots remained on the screen until participants responded or 1.8 sec had elapsed. A tone was played if participants either made an incorrect response or failed to respond within 1.8 seconds (in which case the trial was terminated). Because pilot studies suggested that participants in my pharmacological studies were excessively slow to maintain accuracy, participants were instructed to respond quickly enough that they would make “a few errors” during the task.

In trials in which an emotionally expressive (rather than neutral) face was used, probe dots could be either congruent (appearing in the same position as the emotional face) or incongruent (appearing in the position of the neutral face, opposite to that of the emotional face). There were 56 congruent trials (28 fear-neutral and 28 happy-neutral), 56 incongruent trials (28 fear-neutral and 28 happy-neutral), and 56 neutral trials. The task was counterbalanced for emotion location, probe location, and probe orientation. All participants practiced the task once during a screening session. Each administration of the task began with an additional 35 unscored practice trials, the first twelve of which lacked the face stimuli in order to direct attention to the probe dots.

As is usual for this task, attentional bias scores were calculated for each participant and session by subtracting the mean reaction time of congruent trials from incongruent trials. To control for overall changes in response time, the difference score was divided by the sum of the two measures to create an attentional index. Positive values therefore reflected attention towards the emotional stimuli (vigilance) while negative values indicated attention away from the emotional stimuli (avoidance). To distinguish facilitated responding to salient locations from difficulty disengaging from those locations, I constructed indices comparing congruent or incongruent response times to those from neutral trials. Identical analyses were carried out for fearful faces (putatively threat-related social signals) and happy faces. Incorrect trials and trials with response times greater than 1200 ms were excluded from vigilance analysis. However, number and response times of correct trials were analyzed for each condition and stimulus type to ensure there were no significant differences in these aspects of the task.

Data analysis. Data were generally analyzed in R using linear mixed-effects models with dosing condition as a fixed effect and participant as a random effect using a two-tailed 0.05 level of significance. In order to control for possible sequence effects, linear models initially included a dummy coded term for dosing sequence and a sequence-condition interaction term. When not significant, these terms were removed from the final model. For brevity, results will generally not explicitly state that mixed-effects models use participant as a random effect, which is the case unless otherwise stated. Summary

statistics for the fixed-effects part of the model were calculated with the anova function. When main effects of condition were detected, Tukey's post hoc tests were carried out to compare conditions.

RESULTS

Self-report results

I detected no changes in self-report anxiety. Despite an obvious drug-induced euphoria and positive mood in most MDMA and MDA sessions, there were no effects of dosing condition, session, or sequence on STAI-S or BFNE scores in either study.

Dot probe task

MDA study results. MDA slowed response time. In a mixed-effects model predicting response time from condition, sequence, emotion, and their interactions, there were only significant effects of condition ($F_{1,3728} = 49.98$, $P < 0.0001$) and the interaction of condition and sequence ($F_{1,3728} = 34.55$, $P < 0.0001$). MDA increased response time to 616 ± 47 ms (mean \pm SEM) compared to 592 ± 42 ms after placebo.

The significant interaction of condition and sequence suggested that subjects who received MDA after placebo did not improve in their response times as much as would be expected from repeating the task. This is illustrated with probability density functions for response times in **Figure 3.1**. Participants who received placebo on their first session had mean response times of 631.81 ± 43.02 ms while those receiving placebo in the second session had times of 552.04 ± 37.92 ms. In contrast, those receiving MDA in the second session have similar response times to those receiving MDA on the first session (second session: 628.48 ± 47.29 ms; first session: 604.64 ± 45.59 ms).

Attentional effects of fear-related stimuli. MDA decreased the fear attentional bias for fearful faces (**Figure 3.2 left**). There was only a significant effect of condition ($F_{1,11} = 6.00$, $P = 0.0342$) when I constructed a linear mixed-effects model predicting the fear attentional effect from condition, dosing sequence, and the interaction of the terms. MDA reduced the attention bias by 28.699 ± 4.333 ms compared to placebo. **Figure 3.3** depicts probability distribution functions for response to incongruent and congruent fearful trials in the two dosing conditions.

One participant showed a larger drug effect than others and is depicted as an outlier circle on **Figure 3.2 left**. In order to estimate if this participant exerted undue influence on the results, a simple permutation procedure was conducted by removing this participant's data and repeatedly replacing it with that of another to maintain the sample size. This produced a mean F-value of 5.466, associated with a significant p-value of 0.039.

Because increased response times and would be expected to produce larger difference scores, an attentional bias index was constructed by dividing the difference by the sum of the incongruent and congruent fearful face trials, revealing a similarly significant effect of condition ($F_{1,11} = 5.11$, $P = 0.0450$).

To determine the extent to which this attentional bias reflected a speeded response to congruent fearful faces compared to a difficulty disengaging from incongruent faces, I then constructed analogous indices using neutral trials and either incongruent or congruent fearful trials. This revealed a significant effect of condition on the fearful incongruent vs. neutral index ($F_{1,11} = 6.60$, $P = 0.0261$), showing that MDMA was decreasing the extent to which incongruent fearful faces were slowing performance. This is illustrated in **Figure 3.4**, which plots probability distributions for response times for incongruent and neutral trials for both conditions.

Attentional effects of positively-valenced stimuli. A model that contained sequence and a condition-sequence interaction revealed a significant effect of condition ($F_{1,11} = 6.76$, $P = 0.0265$), with MDMA decreasing the attentional bias for happy face stimuli by 26.95 ± 10.06 ms. However, this was no longer significant ($p = 0.0593$) when using an attentional index score constructed by dividing the incongruent-congruent difference by the sum of the two measures.

MDMA and Citalopram study results. Participants became modestly faster with each session, with mean responses decreasing by 8.51 ± 1.69 ms each session. In addition, both MDMA and citalopram speeded responses (**Figure 3.5**). In a mixed-effects model predicting response time from condition and session, there were significant effects of condition ($F_{2,5692} = 61.168$, $P < 0.0001$) and session ($F_{1,5692} = 41.95$, $P < 0.0001$), with MDMA significantly decreasing response time by 40.34 ± 3.40 ms and citalopram significantly decreasing response time by 20.96 ± 3.35 ms compared to placebo. There was no evidence of a speed-accuracy trade-off, and accuracy remained high in all conditions. There was no effect of dosing sequence.

Attentional effects of threat-related stimuli. MDMA but not citalopram altered the attentional bias for fearful faces (**Figure 3.6**). There was a significant effect of condition ($F_{2,21} = 4.54$, $P = 0.0342$) when I constructed a linear mixed-effects model predicting the fear attentional bias from condition and session. MDMA reduced the attentional bias by 26.024 ± 8.050 ms compared to placebo ($p = 0.00349$). Equivalent results were obtained using attentional bias index scores, with main effects of condition ($F_{2,21} = 5.75$, $p = 0.0102$) and session ($F_{1,21} = 4.93$, $p = 0.0375$). In contrast, there was no significant effect of citalopram, nor was there an effect of dosing sequence.

Attentional effects of positively-valenced stimuli. There was no significant effect of dosing condition on response to trials with happy face stimuli in mixed-effects models analogous to those used to detect the fear effect.

Relationships of dot probe results with self-report measures. I next attempted to correlate fear difference scores and attentional indices with self-report measures of state anxiety and social anxiety. Neither STAI-S nor BFNE scores predicted dot probe performance.

DISCUSSION

In this chapter I report the first attempt to examine the effects of MDA and MDMA on attention to emotional stimuli. I found that increasing extracellular 5-HT using either MDA or MDMA altered the attentional bias for threat-related stimuli in opposite directions. In contrast, I did not detect a significant effect of the SSRI antidepressant citalopram.

I predicted that MDA and MDMA, which increase extracellular 5-HT levels by an impulse-independent mechanism, would decrease the efficacy of a hypothetical phasic threat-sensitive serotonergic signal associated with the amygdala. Results from the MDA study were generally consistent with my predictions. Participants in the MDA study tended to be faster on congruent compared to incongruent trials, suggesting threat vigilance. Administering MDA reduced the disruptive effect of incongruent fearful faces, consistent with hypothesized drug-induced decreases in threat vigilance. However, given evidence of decreased perceptual organization presented in the previous Chapter, it is also possible that the disruptive effect of incongruent faces was decreased by a more general change in perception.

Unexpectedly, alterations occurred in the opposite direction in the study with MDMA in the two studies, although they had different baseline attentional biases. Participants in the MDMA study were initially slower in responding to congruent versus incongruent threat-related stimuli, suggesting threat-avoidant tendencies. Administration of MDMA significantly reversed this bias.

This raises the question of why baseline attentional biases would differ between the two groups of participants. One possible explanation is that, because the participants for the two studies were simultaneously recruited they may have self-sorted, based on the different durations, study drugs, and reimbursements offered. Additionally, the MDMA study required that participants report experiencing residual hangover-like symptoms after MDMA use, while the MDA study had no analogous requirements. Although these symptoms are common (experienced by an estimated 45% of participants in clinical trials [179, 191, 557, 558]), having these adverse MDMA-related symptoms may be related to variation in the serotonergic system and/or to attention to threat-related stimuli [559]. I plan to genotype participants for variants of serotonin-related genes that may influence threat processing [522-529], and this may help explain this population difference.

If the apparently opposite effects of MDA and MDMA both represent the effects of increased extracellular 5-HT, this suggests two possibilities. One is that 5-HT may not provide a phasic threat-sensitive signal but may simply modulate it. In this case, the drugs may have unmasked underlying threat-processing tendencies in the participants. A second possibility is that 5-HT does provide a phasic threat-sensitive signal but that the doses of serotonin releaser, despite producing robust self-report effects, were insufficient to disable it. In principle, administration of different doses of serotonin releasers could clarify this.

I observed no significant effect of the serotonergic drugs on measures of state anxiety. Given that MDMA is purported to decrease anxiety, this lack of effect is somewhat puzzling. While the BFNE has not been previously reported as sensitive to MDMA, MDMA significantly decreased STAI-S scores in one study, but not a second, by Liechti and colleagues [171, 560]. I suggest two possible reasons for failure to detect a consistent effect. First, the STAI-S contains many items that measure anxiety-related physiological arousal, which may decrease the sensitivity of the instrument to MDMA-like drugs, since these drugs produce increases in physiological arousal. Second, the labels used for the Likert scales may have inadvertently decreased the sensitivity of these instruments. Because the lowest points on the scales were labeled ‘not at all’, participants who denied baseline anxiety would have had no way of indicating decreased anxiety after the study drugs were administered. To test this possibility, I am currently administering a modified version of the BFNE in which the middle of the scale range is labeled with ‘normal amount’ and the minimum possible rating is labeled ‘much less than normal’.

I did not detect correlations between dot probe measures of attentional bias and measures of state anxiety. Lack of association between objective attentional bias and self-report measures of state anxiety is consistent with numerous studies showing 5-HT-mediated changes in processing of emotional stimuli can occur without concomitant self-report changes in mood or anxiety [477, 478, 532, 535, 536, 561, 562]. With the exception of these pharmacological states, the published literature appears to associate attentional bias in dot probe tasks with traits rather than states [468-471]. One interpretation of my results is that the frontal-amygdala-serotonergic system underlying the dot probe tasks may trigger but not maintain states of anxiety. In other words, lasting elevations in activity of a threat-detection system may eventually lead to anxiety by consistently biasing processing for negatively valenced stimuli.

The drug-induced attentional changes I detected primarily involved threat-related rather than positively valenced stimuli. Nonetheless, these attentional changes occurred at the same time as drug-induced positive affect. This appears inconsistent with mood congruent attentional biases predicted by some theories of positive affect. Similarly, predictions of increased influence of task irrelevant stimuli made by both the broaden-and-build and affect-as-information theories were not supported, as this should have appeared as increased response times for incongruent trials. However, these results appear consistent with both Carver’s hypothesis that positive mood can be produced by a behavioral-approach or a behavioral-inhibition system as well as my hypothesis that 5-HT selectively modulates the inhibition system. These theories predict independent modulation of the two systems, with broadening of attention being associated with positive affect related to the dopaminergic approach system. Of course, interpreting null results is perilous, and these ideas should be confirmed and extended in d-amphetamine studies that manipulate dopamine and approach systems.

The different drug effects on response time are consistent with my predictions and their proposed pharmacological classifications. As a 5-HT_{2A}R agonist, MDA would be predicted to slow response time [186-189]. For example, the serotonergic hallucinogens psilocybin and DMT both slow overall responding in inhibition of return paradigms [187,

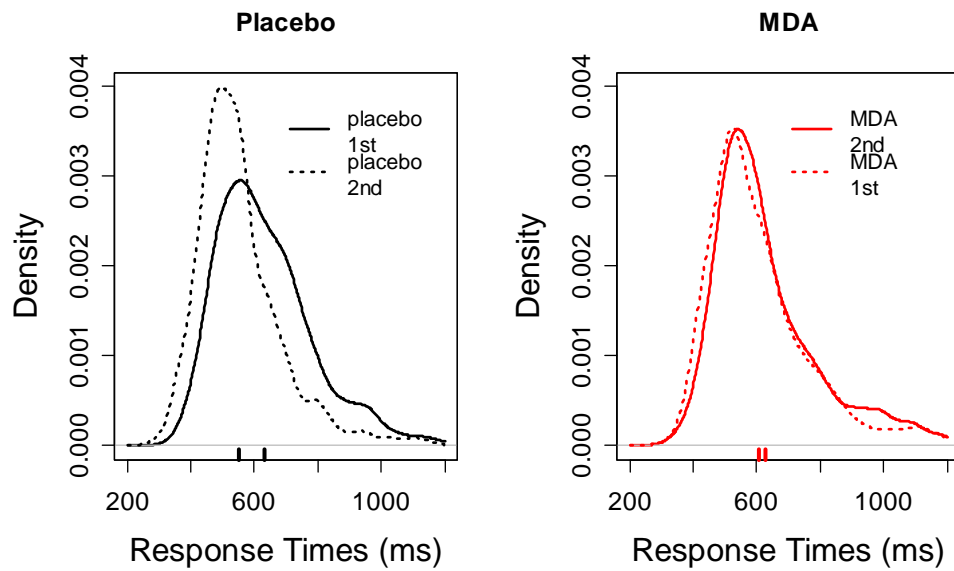
188]. In contrast, Lamers et al. [185] found that 75 mg oral MDMA improved psychomotor performance, such as movement speed and tracking performance in single task and divided attention tasks, while other reports found no effect of MDMA on word-color Stroop [182], continuous performance [183], or digit symbol substitution [184] performance.

Unlike MDA and MDMA, citalopram did not significantly affect attentional bias. Although I did not confirm citalopram concentrations in plasma of participants, I think it is unlikely that a pharmacologically inactive dose was given. The dose used is a standard clinical dose that has been estimated, using SPECT and [123 I]ADAM, to produce $70 \pm 6\%$ occupancy of serotonin transporters [201]. One possibility is that citalopram paradoxically inhibited the firing activity of 5-HT neurons by stimulating autoreceptors, a dose-dependent phenomenon documented in animals [199, 200] that is sometimes used to explain the lag between repeated antidepressant administration and relief of psychiatric symptoms. However, this appears to require higher doses in animals. Furthermore, others have detected seemingly related effects of the same dose of citalopram in volunteers [477, 561]. An alternative possibility is that MDMA users may have decreased sensitivity to citalopram, a possibility that is consistent with evidence of serotonergic changes reviewed in the previous Chapter.

Faces with happy and fearful expressions are commonly used as stimuli in research such as mine and are commonly discussed as differing only in emotional significance. However, there are also inescapable low-level differences in these stimuli that may also influence their processing by visual and attentional systems. Influence of these low level differences cannot be excluded in the current studies. It would alternatively be possible to use upright and inverted fearful faces to study effects of threat-related stimuli on dot probe performance, although one would then need to control for the unusual configuration of inverted faces.

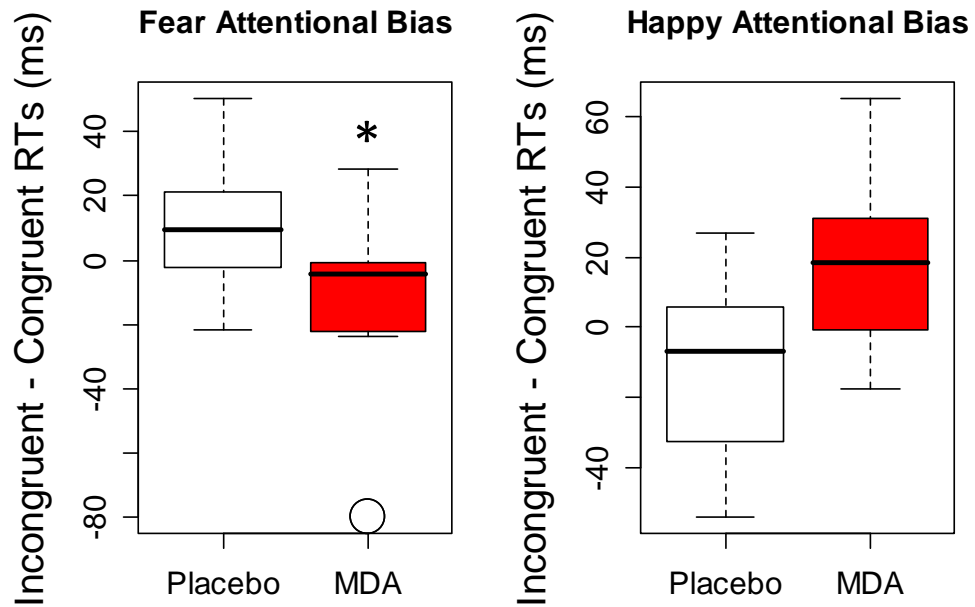
In conclusion, I conducted the first study of the effects of MDA and MDMA on attention to emotional stimuli. Using a dot probe task, I found preliminary evidence that MDA and MDMA modify processing of threat-related stimuli. These effects appear unrelated to state anxiety and are generally not consistent with theories of the attentional effects of positive affect.

Figure 3.1: MDA slows dot probe task response times



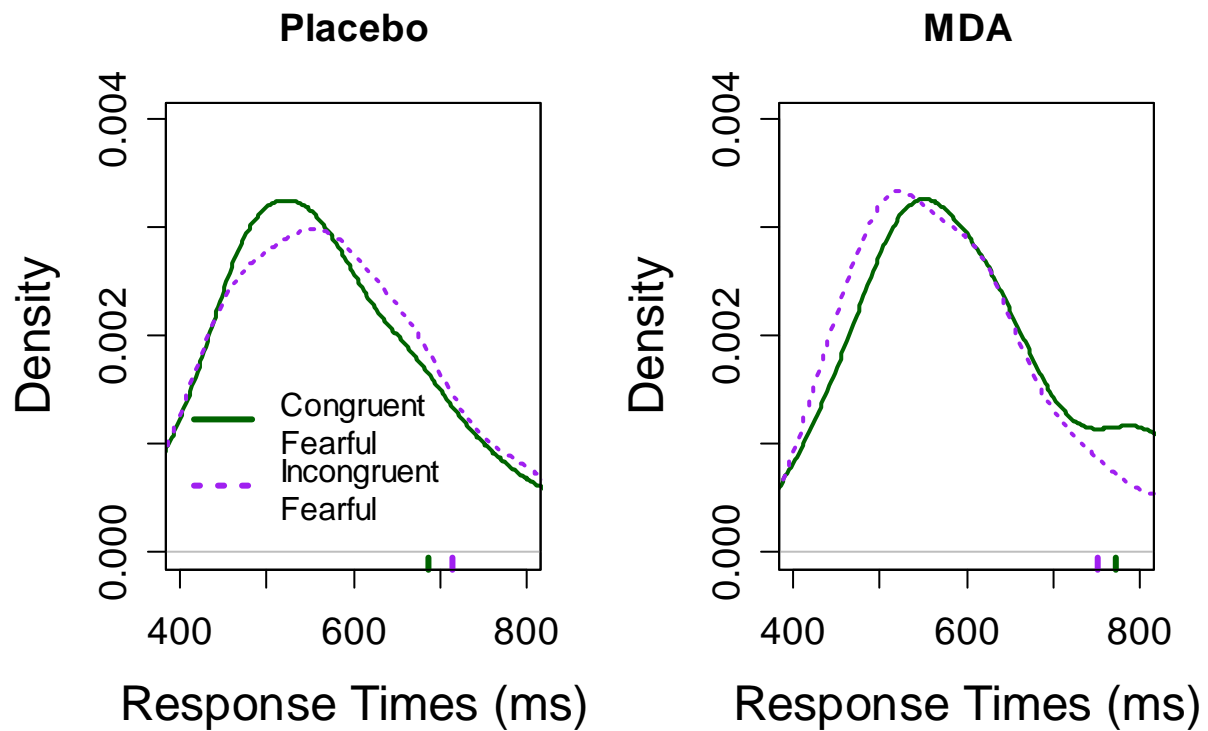
Probability distribution of response times on the dot probe task shown by dosing condition (left black for Placebo, right red for MDA) and sequence (solid for placebo first, dotted for MDA first). Vertical ticks under the plots indicate mean response times.

Figure 3.2: MDA decreases attention to fearful faces



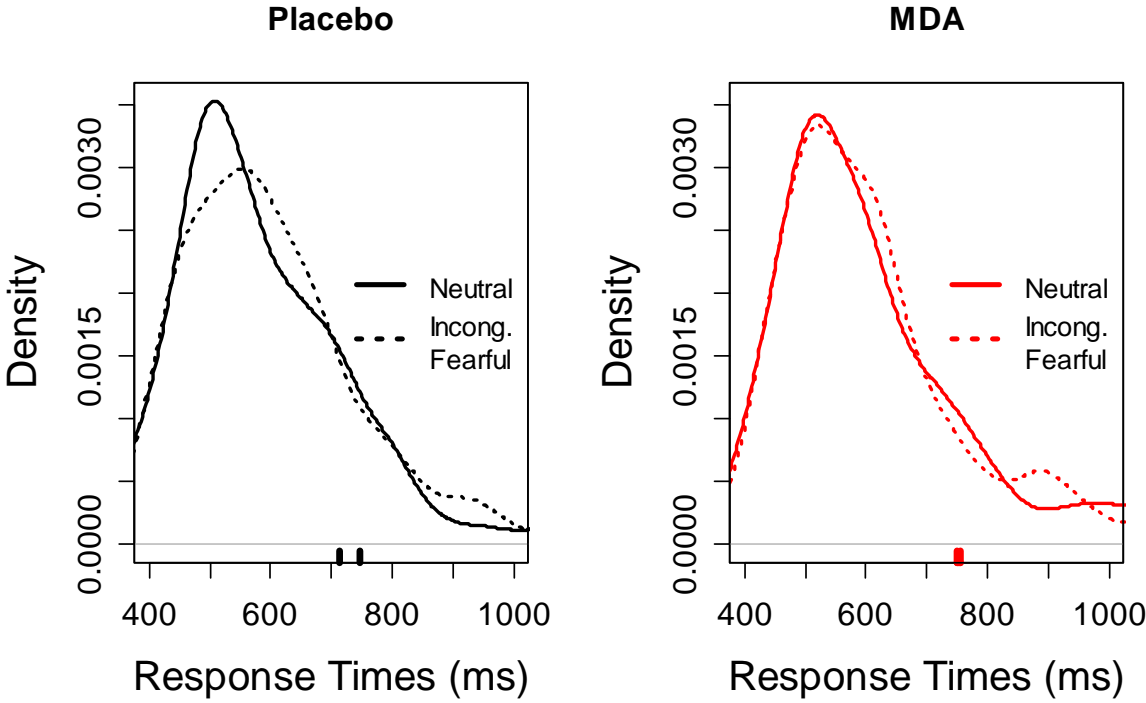
Box and whisker plots show attentional effects on response times (RTs) for fearful (left) and happy (right) stimuli for Placebo (white boxes) and MDA (red boxes). Dot on left plot MDA condition indicates an outlier individual who showed a large effect.

Figure 3.3: MDA shifts response time distributions for congruous vs. incongruous fearful faces



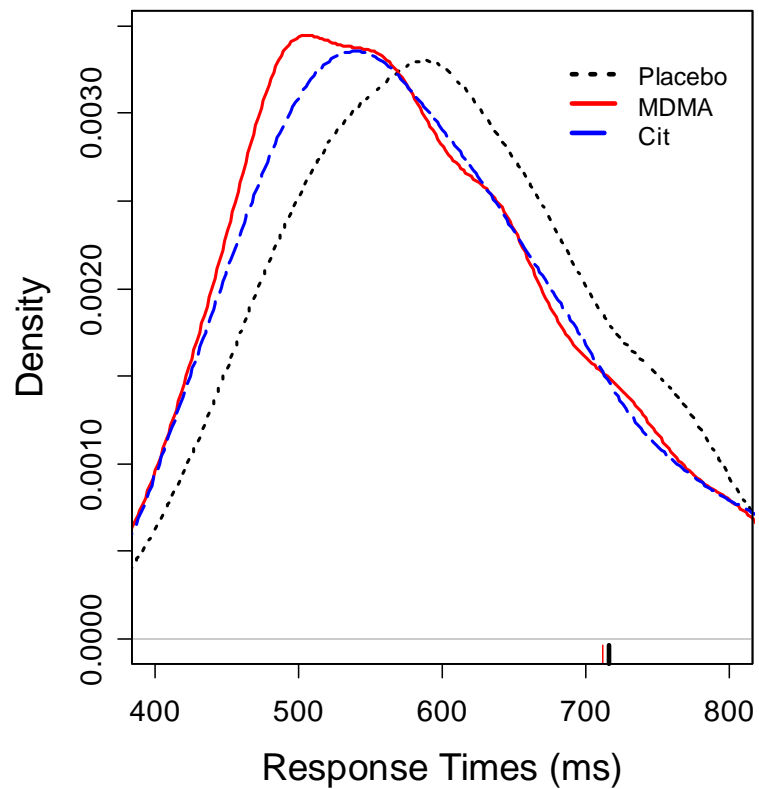
Probability distribution of response times on the dot probe task shown by dosing condition (left for Placebo, right for MDA) and congruence (solid green for congruent fearful, dotted purple for incongruent fearful). Vertical ticks under the plots indicate mean response times.

Figure 3.4: MDA reduces differences in response times between neutral and incongruous fearful faces



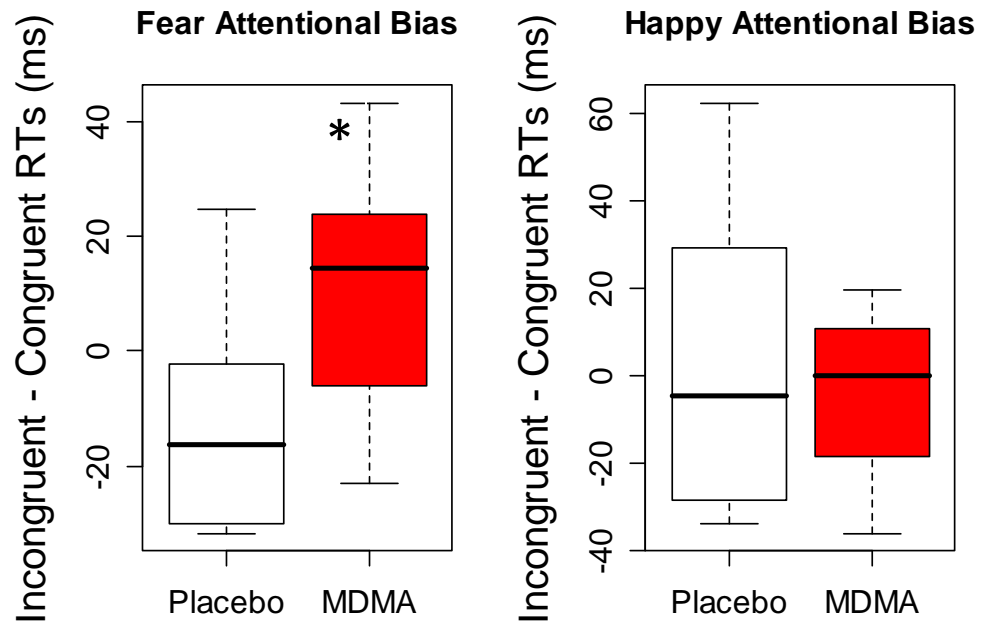
Probability distribution of response times on the dot probe task shown by dosing condition (left for Placebo, right for MDA) and congruence (solid for neutral, dotted for incongruent fearful). Vertical ticks under the plots indicate mean response times.

Figure 3.5: MDMA and citalopram decrease response times



Probability distribution of response times on the dot-probe task shown by dosing condition (dotted for Placebo, red solid for MDMA, blue solid for Cit (citalopram)). Colored vertical ticks under the plots indicate mean response times.

Figure 3.6: MDMA shifts attentional bias for fearful faces in the opposite direction as MDA



CONCLUDING COMMENTS

In my first Chapter, I described findings of an online questionnaire that documented the prevalence, symptoms, and relationship to drug use of persisting unusual visual phenomena in hallucinogen users. Most participants reported having experienced drug-free visual experiences that resembled hallucinogen effects. The probability of experiencing constant or near constant symptoms was predicted by greater past exposure to specific hallucinogens, including LSD. Although symptoms were common, few found them distressing or impairing enough to consider seeking treatment.

In the survey, I saw a puzzling pharmacological diversity of drugs associated with persisting unusual visual phenomena. These included the serotonergic hallucinogen LSD, the antitussive dextromethorphan, and the KOR-agonist-containing plant *Salvia divinorum*. This made it seem unlikely that these phenomena could be explained by damage to one type of cell in the visual system, contrary to some theories. While NMDA antagonists can produce lesions in rodents [244], and MDMA can cause long-term monoaminergic changes in primates and rodents [170], it is notable that no reports confirm persisting changes in receptors or neurotoxicity in animals or humans after exposure to serotonergic hallucinogens like LSD.

In Chapter 2, I examined theories of the mechanisms of visual hallucinations in more detail. Hallucinations are typically explained by a combination of three factors, none of which are mutually exclusive: alterations in cognitive functions; loss of sensory or perceptual ability; and abnormally increased neural activity. The interplay of factors that can contribute to hallucinations appears to make the findings of Chapter 1 more understandable. If hallucinations are the result of a hierarchical inferential process, errors often are likely to have similarities that are partly independent from their biological sources. After all, the best-guess conclusions should be heavily influenced by the statistics of inputs to perception. Similarities of hallucinatory syndromes induced by different drugs or neurological changes may exist because of the adaptations of individual organisms to similar environments.

I investigated mechanisms of visual hallucinations from serotonergic hallucinogens by measuring the visual and perceptual effects of MDA in a double-blind placebo-controlled study. I found that MDA significantly increased closed-eye visuals (CEVs), although with considerable individual variation. Magnitude of CEVs after MDA was associated with lower performance on measures of contour integration and object recognition, supporting a hypothesized link between hallucinations and impairments in sensory or perceptual processing. I was less successful at linking the phenomenology of MDA to the Ermentrout-Cowan model of visual hallucinations or potential changes in efficacy of top-down processes during perception. This may partly be because MDA does not produce visual hallucinations to the degree that some other hallucinogens do. The more robust visual changes produced by psilocybin, mescaline, or LSD may be more amenable to these measures. Hopefully, further studies with these compounds will prove informative.

I attempted to quantify the general categories of CEVs induced by MDA using very simple visual-analog items; the more detailed phenomenology of these visual experiences

was not quantified. However, participants described both prosaic and fantastical percepts. One question raised by these visual changes is why the inferential process that underlies perception makes such seemingly improbable inferences. One possible explanation is that closed-eye visuals are as much a type of mental imagery as a type of perception and are therefore less constrained by the general context of the perceiver. Exploring the effects of hallucinogens on mental imagery could be a promising direction for future research.

Another possibility is that a system that infers visual context may be impaired. Work by Bar and colleagues [403, 404] provides evidence that low spatial frequency information is rapidly projected from early visual areas to the prefrontal cortex, where it activates an ‘initial guess’ of the visual input that is then provided to the temporal cortex to be integrated with bottom-up visual information being processed in that area. As I noted in Chapter 1, if there are consistent alterations in the visual system of people with these persisting visual phenomena, it seems more likely that they involve the magnocellular rather than parvocellular visual pathway. The relative lack of form perception deficits, the frequency of motion-related complaints, and an apparent association of symptoms with low-light and peripheral visual fields all seem arguably more consistent with decreased magnocellular fidelity. Intriguingly, there is evidence of a magnocellular bias to serotonergic innervation of the primary visual cortex [245] and evidence that individuals at risk for psychosis may have magnocellular dysfunction [252]. Thus, I speculate that impairments to a fast magnocellular signal might impair initial estimates of the visual scene and lead to contextually unlikely inferences.

Finally, in Chapter 3, I described experiments on the effects of serotonergic drugs on attention to emotional stimuli. Using a dot probe task, I found preliminary evidence that MDA and MDMA modify processing of threat-related stimuli. Superficially, this seems different from the study of hallucinations, with the primary link being that MDA-induced hallucinations are thought to be caused by changes in overall serotonergic tone in the cortex and altered attention to threats by changes in phasic serotonergic signaling. However, assessing potential threats is also a fast inference that is thought to rely on low spatial frequency information. Although I hypothesized that serotonin releasers impair a phasic threat-sensitive signal, they could also be seen as impairing an inferential process. It may be revealing for future studies to consider whether cognitive effects of serotonergic drugs might have some common underlying basis relating to inference.

Research of the sort performed in this dissertation proceeds slowly because of the complex social context in which it occurs. Studies with controlled substances are carefully evaluated in terms of risks and benefits to participants and society. Research is most clearly defensible if it, in part, addresses clinically relevant questions relating to morbidity or mortality. These are important and appropriate considerations.

Nonetheless, resulting studies are expensive and not always ideally suited for understanding phenomenology and consciousness. This complexity relates both to the participants and the drugs used. Participants typically have difficulty quantifying their histories, and this may influence study measures. The available drugs that are used nonmedically and are appropriate for human research, such as MDA and MDMA, often

have complex pharmacology that makes mechanistic inference difficult without results from studies of complicated drug interactions.

Over time, as science and society learn more about the neuroscience of serotonin, this will change. In the last decade alone, the field of researchers studying pharmacological serotonin releasers and 5-HT_{2A}R agonists has grown. At the same time, the range of published topics has expanded dramatically. The challenge is no longer figuring out Byzantine regulatory systems; the challenge is now figuring out Byzantine nervous systems and using the results to help humanity. I hope that the research described in this dissertation (and associated peer-reviewed papers) will contribute to this process.

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