

Selective 5-HT_{2A} agonist hallucinogens: A review of pharmacological interaction and corollary perceptual effects

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Abstract/Summary

The most potent tryptamine hallucinogens – such as DMT, psilocybin, and LSD – are all active at the 5-HT_{2A} receptor subtype and all produce similar visual perceptual results that are immediately recognizable as uniquely psychedelic. Although it is widely accepted that selective serotonin receptor subtype _{2A} agonism is directly responsible for producing the distinct hallucinations seen on a psychedelic trip, no single theory has yet explained why this is so. Utilizing what we know about psychedelic tryptamine receptor interaction, sensory processing circuits in the neocortex, and EEG scans of psychedelics in action, this review will propose a novel multi-state theory of psychedelic action which invokes a variety of neural processing mechanisms, including phase-coupled neural oscillators; network excitation, disinhibition, and destabilization; recurrent feedback excitation; and neural circuit spike synchrony and brainwave cohesion to close the knowledge gap between the pharmaceutical interactions of selective 5-HT_{2A} hallucinogens, their direct effects on perception and consciousness at varying dose ranges, and their potential long-term adverse effects.

Keywords: hallucinogens, psychedelics, serotonin, 5-HT_{2A} receptors, layer V pyramidal neurons, disinhibition, recurrent excitation, thalamocortical feedback loops, interareal feedback loops, corticocortical feedback loops, neural spike synchrony, asynchronous ESPCs, late ISPCs, phosphenes, neural oscillators, coupled oscillators, pharmacology, perception, consciousness, OBEs, NDEs, binding, cognitive theory.

Layer V Pyramidal Cells and 5-HT_{2A} Mediated Feedback Modulation

The most potent and most visual of all hallucinogens are the psychedelic tryptamines, which have chemical structure similar to serotonin and have been shown to be directly active at the 5-HT_{2A} receptor subtype, with slightly lesser affinity at the _{2C} subtype[1]. Within the brain the highest density of 5-HT_{2A} receptors are expressed on the dendrites of cortical Layer V pyramidal cells[2-3], and the highest density of Layer V dendrites project upward into the dendritic arbors of cortical Layer I, the very outward surface of the cortex. The dendritic arbors of the neocortex contain the highest density of neural receptors in the brain, and are responsible for top-down detail analysis of incoming sensory data[4]. All layers of the neocortex interact with Layer I dendritic arbors – either sending or retrieving impulses in arboreal feedback loops – in order to maintain consistent sensory analysis of external reality from moment to moment. Layer V axonal projections, which connect to lower areas of the brain as well as laterally across the entire cortex, are one of the primary conduits for binding information localized in one area of the neocortex to information localized in another area of the cortex.

Layer V pyramidal cells are unique in the cortex in that they mediate multiple pathways of feedback excitation in perceptual analysis. For example, in the visual cortex alone Layer V pyramidal cells are responsible for synchronizing corticothalamic activity with the thalamic nuclei via descending axons; they also mediate feedback excitation in interlaminar circuits via recurrent collaterals ascending back up through Layers I-IV; they mediate reciprocal interareal connections via laterally branching arboreal and basilar dendrites; and they mediate afferent corticocortical signal flow along the dorsal and ventral processing streams[5-6]. To illustrate the importance of Layer V cells in mediating cortical signal flow and feedback, I offer this quote from Edward Jones on synchrony in thalamocortical circuits:

"The capacity of the layer V corticothalamic projection to bring activity in one cortical region to thalamic nuclei that project to adjacent regions, and even to distant regions located in other lobes of the cerebral hemisphere, could extend the binding process by providing a basis for unifying activity in the somatosensory and motor cortex during movement performance (Ribary et al. 1991; Murthy & Fetz 1992, 1996a,b; Sanes & Donoghue 1993), and in parietal areas engaged in perception with that in frontal areas engaged in planning strategies for action (Tononi et al. 1992; Lumer et al. 1997). Corticocortical connections undoubtedly play a prominent part here as well but they would run parallel to a system of corticothalamic loops in spreading activity across the forebrain."[5]

It should be taken as evident that Layer V pyramidal cells are essential in mediating multiple layers of cortical and thalamocortical feedback in order to sustain brainwave cohesion and neural spike synchrony across the entire brain, a process referred to as sensory binding. Given the various circuit functions of Layer V pyramidal cells and the prevalence of 5-HT_{2A} receptors mediating these neurons, the notion that 5-HT_{2A} selective agonists can act as both cortical feedback amplifiers and/or interrupters at varying dose ranges is not only likely, it would also explain a wide range of perceptual effects associated with the classic psychedelic trip.

Circuit Excitation: Phosphenes, Asynchronous ESPCs, and Low-Dose Hallucinations

Since hallucinogenic tryptamines produce a variety of visual hallucinations at differing dose ranges it is helpful to break down these subjective results by dose range to gauge the level of cortical circuit excitation by corresponding perceptual effects. Even at low doses the most commonly reported visual effects of tryptamine intoxication are pulsating or slowly-rotating closed-eye geometric mandalas, tunnels, and spider webs, also known as phosphenes. Phosphenes are visual artifacts of the spatially organized neural transforms that take place between the spherically organized receptor cells of the retina and the grid-like columnar processing cells in the visual cortex. This visual pathway transformation translates incomplete rings of color and intensity data captured along the retina into the fine lines, shades, and fills we perceive in waking consciousness, yet when the visual processing pathway becomes excited and neural coupling in the thalamocortical loop destabilizes, visual artifacts of these spatially organized networks appear spontaneously within our closed-eye field of vision.[7,8,9]

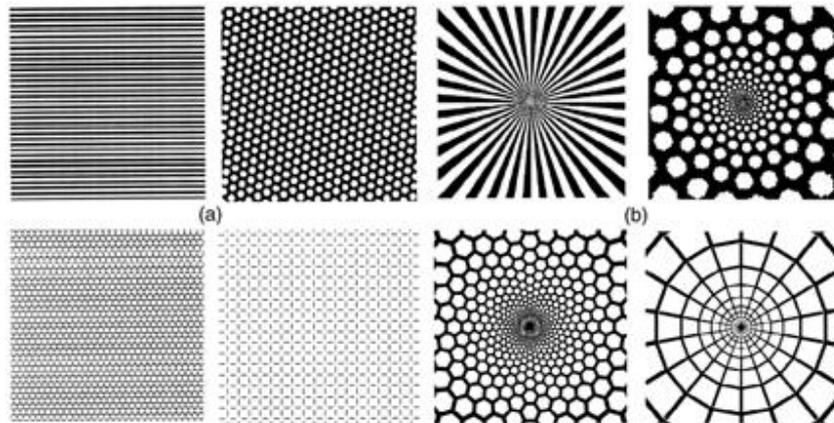


Figure 1. Phosphenes and Excitation in Cortical Loops: The above panels show bifurcating patterns in spatially oriented grid-like cortical networks (a) and ring-link retinal networks (b). The top panels show patterns arising from distance-dependent connections; the bottom panels show distance- and orientation-dependent connections (Bressloff, et. al).

Boris Gutkin describes the emergence of spontaneous geometric patterns due to excitation and instability in recurrent visual circuits thusly:

"Ermentrout and Cowan showed that spontaneous symmetry breaking in spatially organized cortical networks could account for coarse spatial activity patterns perceived during hallucinations. More recently, Bressloff. et al. have incorporated coupling between orientation-sensitive cells to explain other types of more complex hallucinatory patterns... Generically for a random symmetric network, we expect either a transcritical or pitchfork bifurcation leading to a single excited mode reflecting the organization of the random network. If the effect of hallucinogens or other external stimuli is to produce an overall increase in excitability of the network, then is it possible that the background state can become unstable leading to a spontaneous pattern of activity reflecting the associative organization of the recurrent network." [10]

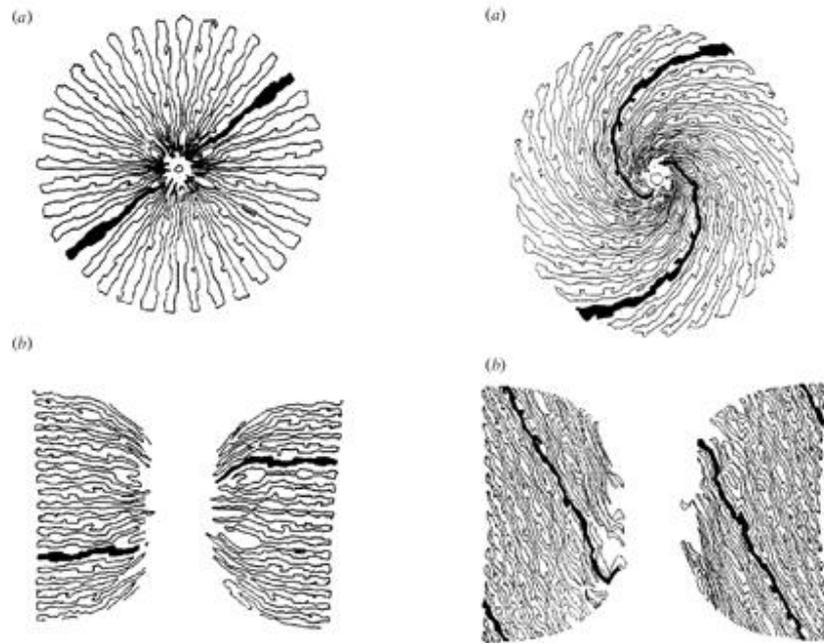


Figure 2. Spatial organization of retinal neurons. On the right is the action of the retinocorticalmap on the funnel form constant. On the left is the action of the retinocorticalmap on the spiral form constant. For both images (a) represents the image in the conical visual field, (b) represents the flattened V1 map of the image. (Bressloff, et. al).

In the framework of this discussion we will assume that the phosphenes seen during low-dose tryptamine sessions are the artifacts of visual pathway excitation and destabilization in thalamocortical feedback loop due to 5-HT_{2A} receptor interaction, and that the likely origin of this destabilizing affect is the corticothalamic axonal projections from V1 (visual cortex area 1) Layer V pyramidal cells. Although this destabilizing effect could be due to simple 5-HT_{2A} agonism or modulatory interruption at the presynaptic neuron, there is also evidence that this excitation may be due to an asynchronous release of glutamate from Layer V pyramidal cells, resulting in the generation of spontaneous excitatory postsynaptic currents (EPSCs) following each axonal spike.[11] This effect is presumably not entirely localized in the visual cortex, allowing for similar network-based tactile and audio hallucinations, such as tingling skin or buzzing and ringing in the ears, to begin overloading actual sensation. These effects would all indicate a mild excitatory feedback cascade within the overall neural network, resulting in phantom network noise and an increase in respiration and stress hormones to support the growing neural energy output.

In addition to phosphenes and closed-eye geometric visuals, there are other general perceptual effects one would expect to see as a result of excitation and instability in visual thalamocortical feedback loops, such as strobing or pulsing of light intensity and the perception of halos and softening of contrast in line resolution around light sources. The reactionary dilation of the pupil may also occur as an autonomic result of excitation and instability along the visual pathway. There is also some evidence that reciprocal connections between areas V1, V2, and V3 in the visual cortex are responsible for discrimination between figure and background detail in depth perception[12], and it is easy to understand how excitation or loss of coupling stability in these connections could lead to the animated shifting of depth and perspective of objects in the visual field, another classically reported effect of low- to mid- dose psychedelic trips.

Disinhibition and Low-Dose Perceptual Distortions

Beyond the flickering lights and geometric patterns seen in low-dose tryptamine hallucination, mid-dose psychedelic hallucinations generally involve open-eye fluid distortions in the rendering of line, shape, texture, and depth. Subjects under a sub-peak dose often report seeing breathing walls, creeping carpets, melting textures, and flickering geometric patterns crawling over every surface. These effects are all similar in that they represent a destabilization in the visual cortex's ability to hold sharp line, contrast, and texture detail in visual memory, and demonstrate a clear drifting or leaking of contrast information both laterally and radially across the cortex. This fluid-like drifting in the visual field is most prominent in the periphery where the retinal blind-spots are working with incomplete data to begin with.

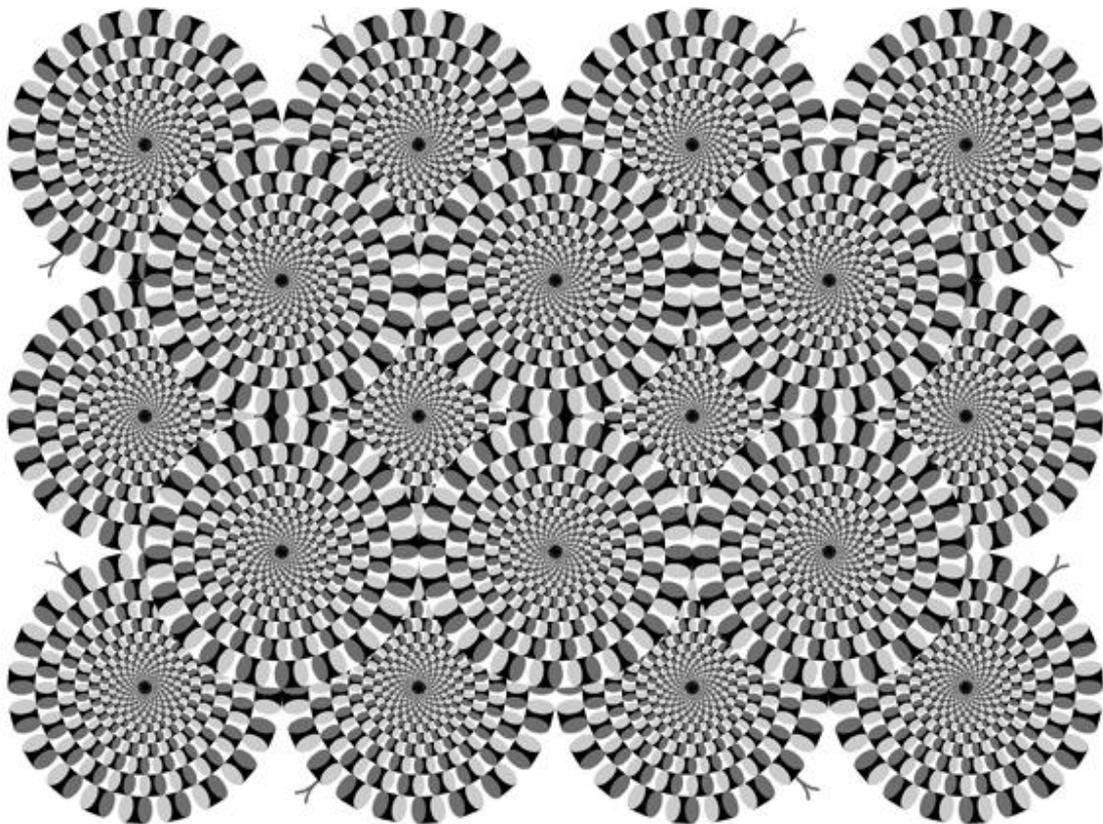


Figure 3. Akiyoshi Kitaoka "Rotating Snakes" illusion presents an example of radial drift illusion caused by line ambiguity in peripheral visual field. Even though this image has been downsized and reproduced in black and white, if you stare at the center of this image the illusion of rotational drift in the periphery is obvious. This illusion is most likely due to a bug in the cortical lateral line-resolution process which causes ambiguous data in the visual periphery to remain unresolved, thus lines cannot hold and instead creep and drift, creating the illusion of gradual radial movement. This creeping of line and shade in the periphery is similar to animated hallucinations seen on a light psychedelic trip.[22]

Hallucinations of creeping line, depth, and shadow are most likely caused by a loss of lateral inhibition within circuits in the peripheral visual field, and we can only assume that 5-HT_{2A}

selective agonism is either directly or indirectly responsible for this disinhibition. One would also assume that the level of disinhibition and lateral drift in the visual field would be proportional to the dose of hallucinogen, and this assumption is generally proved correct by individual reports of hallucinogenic use. While at lower doses there may be only slight wiggling or drifting to the animation of line and depth, at higher doses the lines between otherwise solid forms may actually appear to melt and swirl into one another.

These classic psychedelic hallucinations are all attributable to lateral disinhibition and local bleed-over excitation in the visual field. The loss of lateral inhibition may be attributable to the ESPCs caused by asynchronous glutamate leakage discussed earlier. But in addition to this theory, Leonard Kass proposed what was termed the “Presynaptic Uptake Blockade Hypothesis for the action of LSD” in 1983. In short, Kass' research led him to believe that LSD blocks presynaptic uptake of 5-HT at the lateral inhibitory synapse, thus destabilizing lateral inhibition and allowing bleed-over excitation along the sensory processing pathways.[13]

Given the range of serotonergic functionality in the brain we must not ignore the possibility that 5-HT_{2A} selective agonists may have multiple actions at multiple sites, serving to both dampen localized lateral inhibition while simultaneously promoting feedback excitation across the entire cortex. This dualistic effect would become synergistic at higher doses, serving to boost overall brain excitation by flooding disinhibited networks with uninhibited or runaway feedback processing loops. With sufficient loss of lateral inhibition in the visual cortex, even a small amount of perceived motion would cause a standing wave of recurrent excitation along the thalamocortical loop, leading to ghost-like afterimages which fade in the wake of moving objects. This recurrent “echo effect” would presumably apply to all sensation introduced to the sensory processing system, not just visual, similarly explaining a wide variety of subjective effects.

Recurrent Excitation and Sub-Peak Hallucination

Disinhibition alone may account for a variety of psychedelic experiences, but if we are to follow the notion that Layer V pyramidal neurons are disinhibited and prone to excitability under the influence of selective 5-HT_{2A} agonists, then we must step back and look to all the feedback connections these cells mediate in order to understand how disinhibition and recurrent excitation at this centralized pathway could potentially affect the entirety of consciousness.

The Thalamocortical Feedback Circuit

Layer V pyramidal cells mediate the thalamocortical feedback circuit via descending axons, making Layer V neurons the primary route of thalamocortical feedback circuit. This feedback circuit is primarily used for top-down focus and attention-driven discrimination of incoming data sets. We have already discussed what might happen if the coupling was destabilized in this circuit, including the emergence of phosphenes, frame flickering, frame rotation, and other simple frame translation errors.

The Interlaminar Feedback Circuit

Layer V pyramidal cells are responsible for mediating sensory feedback with the layers of cortex via ascending recurrent collaterals, making them the primary driver of the interlaminar feedback circuit. This circuit is characterized by bottom-to-top vertical feedback between dendritic arbors

in cortical Layer I and the inter-networked layers of II-V. In the alert waking state immediate perception does not require much interlaminar feedback excitation. Recent research has shown that the bulk of immediate sensory processing occurs as a constant stream of feed-forward sweeps and fills[15]. Top-down feedback in this circuit only kicks in when a particular data set is ambiguous, salient, or requires more detail articulation. Top down feedback excitation serves to narrow cortical focus in order resolve fine detail in salient data sets. If this feedback circuit were excited by hallucinogens, there would be an overall increase in intensity, perceived importance, and data resolution on all incoming sensation. If this feedback excitation were to occur while local interneurons were simultaneously disinhibited, sensory feedback processing would run the risk of over-articulating all incoming data into fractally receding groups of complex embedded patterns. The imaginary extrusion of lines and the perception of deeply embedded fractal patterns in random textures is another classic mid- to high-dose psychedelic hallucination.

The Interareal Feedback Circuit

Within the visual cortex, Layer V cells mediate reciprocal connections with visual sub-processing areas, such as V1, V2, and so on, which allow for a variety of specialized interareal processes[12]. Much like the interlaminar circuit, feedback excitation in this circuit would intensify depth and foreground-figure detail while simultaneously warping the perspective of visual space. A loss of stability in this pathway could lead to fish-eye perspectives, with stationary objects in the visual periphery appearing to either lean forward or recede backward in fluid wave-like rhythms. Similarly, depth perception would appear to recede off into infinity wherever light contrast was such that the ability to discriminate between foreground and background detail was lost.

The Corticocortical Feedback Loop

Moving onward from the visual cortex to higher processing centers along the visual pathway, Layer V pyramidal neurons are once again responsible for mediating corticocortical circuits along both dorsal and ventral streams, all the way up to the multi-modal sensory convergence areas in the pre-frontal cortex (PFC). Destabilization along this all-important binding pathway would allow for a multi-layered cascade of top-down excitatory feedback loops with extreme perceptual results. This is where 5-HT_{2A} selective agonists stop being strictly perceptual and begin to affect the entirety of consciousness. Cross-lobe reciprocal pathways are essential for mediating our real-time multi-modal awareness of reality and the self. When these pathways become excited and begin to destabilize the perceptual effect goes beyond visual hallucination and becomes profoundly disorienting. A subject with heightened excitation along these pathways would experience very complex and disturbing changes in reality, such as visual frame-skipping; memory loss; memory gaps; temporal distortion; time lags; obsessive thought loops; logic traps; the inability to match words to objects; the inability to maintain a train of thought over a few seconds long before it repeats itself; the simultaneous “filling up” or overload of all senses; and the overwhelming urge to shut-down, hide, or recede from reality.

In contrast, once these cortical feedback circuits are fully interrupted and decoupled the subject loses all sense of self, time, and place; becomes profoundly quiet and peaceful inside; becomes infinitely large; floats through an idealized spirit world; and finds existential oneness with the universe. This state is often referred to in psycho-mystical terms as ego-death, the no-mind state, or transcendence. While in this state the subject is perfectly fine and appears to be meditating or in a light trance. The subjective experience of this state is similar in many ways to classic descriptions of out-of-body (OBEs) or near-death experiences (NDEs).

The subjective hallucinogenic and mystical effects of cortical decoupling are best demonstrated in emergent ketamine-induced states, where the visual cortex decouples from external reality and a boundless, formless dream-space appears to open. The mystical effects of cortical decoupling are described in similar terms by stroke victims, epileptics, meditation gurus, drug users, and people who use other technology such as transcranial-magnetic stimulation (TMS) to interrupt phase-coupled cross-lobe activity. At high doses 5-HT_{2A} agonists can create similar decoupling results, yet not as quickly or drastically as the anesthetic ketamine. With orally-ingested psychedelics the journey through excitation to network destabilization to feedback overload to complete decoupling is a long and arduous journey taking many hours to reach full effect. In contrast, smoked or IV DMT administration can compress this process into about five minutes, with another ten or so minutes for the drug to metabolize and the process to entirely reverse itself. This rapid shifting through multi-phase brain states in such a short period of time is perhaps why DMT is considered so dramatic.

Brainwave coherence and multi-phasic hallucinatory states

Generally there are two different types of high-dose psychedelic experience; the closed-eye peak and the open-eyed peak. The closed-eye peak is very similar to a trance or lucid dream state in which the subject reclines, relaxes, and experiences fluid, highly-detailed dream-like visions while still retaining some small sense of self and the waking mind. The open-eyed peaking state is very similar to manic psychosis in which the subject loses touch with reality; sees and hears fully-formed waking hallucinations; becomes disoriented, manic, and paranoid; and generally behaves irrationally and with exuberance. In most clinical studies these open- and closed-eye states are considered to be the same; they are both "hallucinatory" psychotic states. However, there is a large difference between these states both practically and experientially, and this may lead to some confusion when attempting to analyze the "hallucinatory" brain state as if it were a single state. In a paper on hallucinogen persisting perception disorder (HPPD), Henry Abraham describes the differing states of regional brainwave coherence in open- and closed-eye states thusly:

"In the eyes-open state in HPPD subjects, widespread reduction of coherence was noted. However, upon eye closure, the occipital region demonstrated augmented regional coherence over many frequencies but with reduced coherence of the occipital region to more distant regions... We speculate from coherence and known clinical and psychophysical data that, in HPPD, there is widespread cortical inhibition in the eyes-opened state, but localized and isolated occipital disinhibition upon eye closure, a state known to facilitate hallucinatory experiences. An analogy is drawn to findings in the interictal and ictal epileptic focus. In HPPD, we speculate that occipital EEG hypersynchrony resulting from increased regional coherence, when coupled with relative isolation of visual cortex, especially upon eye closure, facilitates hallucinations and illusions." [16]

In other words, the closed-eye hallucinatory state is one of isolated occipital disinhibition where the visual cortex is allowed to "run free" with an uninhibited visual stream of consciousness, demonstrated by high-power regional coherence. Conversely the open eye state inhibits this regional coherence and attempts to lock visual cohesion with other areas of the brain, allowing for more controlled focus of external sensory detail. Generally speaking, loss of overall coherence in both of these states would lead to loss in the ability to hold proper multi-modal focus, causing low-level detail drifting and other similar perceptual ambiguities.

Because wiring up a subject with electrodes takes some amount of time, and because lying down and closing the eyes requires little or no physical activity (which can disrupt EEG scans), most EEG studies of subjects under the influence of psychedelics have focused on this closed-eye hallucinatory state. And much like a lucid dreaming trance state, we would expect the brainwave activity of the subject in the closed-eye hallucinogen peak to actually drop in power across all bands, which it appears to do in some studies.[17] However, other studies show that alpha and theta brainwave activity actually increases localized in the visual cortex[18], that blood-flow and neural firing rates increase in the prefrontal cortex and limbic complex[19], and that brainwave coherence between occipital and other regions of the brain may actually spike up into the gamma range[14]. All of these contrasting reports point to conclusion that the closed-eye hallucinatory state can be a meditative low-activity state, an engaged high-activity state, an emotionally salient state, and emotionally removed state, or a hyper-coherent state of multi-modal synesthesia. The fact that a single drug or drug type can produce such contrasting but dramatic results in brain activity across multiple brain areas suggests a multi-action, multi-state model for psychedelic action consistent with the process of circuit excitation, network destabilization, cross-lobe decoupling, and subsequent re-coherence of brain activity based on the subject's unique behavioral state.

Runaway Feedback Excitation and Multi-Stable Phase States

In a multi-state model of psychedelic action based on lateral disinhibition and runaway feedback excitation, at high doses one would expect neural activity to feedback upon itself and naturally accelerate into higher and higher levels until the network tops out at peak performance, washes entirely white with glutamic overload, and subsequently decouples and down-regulates at a lower energy state. This feedback overload state is consistent with subject reports of peak psychedelic experiences in which the subject "whites out" into a state of sensory overload. While feedback overload may be inevitable and unstoppable in most high-dose trips, on smaller psychedelic doses the brain shows the unique ability to "hold" or "lock" high-energy phase states for extended periods of time before topping-out or down-regulating to levels approaching baseline.

To demonstrate how this process of high-activity neural synchronization might occur, I borrow the research from Erik D. Lumer, and will reprint some comments from his 1997 paper on neural synchrony in cortical loops:

"We showed that interareal corticocortical loops and corticothalamic loops are responsible for coordinating fast activities over widespread territories (Lumer et al., 1997). Interrupting activity along those loops dramatically reduced the amount of synchrony observed between cortical areas or between the cortex and the thalamus. In the present work, by parametrically increasing the degree of activation of these loops, we saw that a critical amount of activity had to be reached in order to produce synchronous firing among neurons along these loops. The sudden increase in the degree of synchrony and of the effectiveness of synchrony when the stimulus intensity reaches a certain level is associated with a sudden increase of the variance of neural activity. This abrupt, nonlinear effect is characteristic of a non-equilibrium phase transition." [5]

In other words, increased sustained excitation in any set of neurons along neural feedback loops will eventually reach a tipping point beyond destabilization which causes the neurons within the circuit to re-synchronize with the excitatory pulse-driver. Thus, if low dose hallucinogenic states can be described in terms of excitation and destabilization of coupled

feedback oscillators along cortical loops, a high-dose or peak psychedelic state may be described in terms of a phase-transition from a low-energy waking state to a high energy waking/dreaming state, a state which can be measured in terms of both raw neural spiking and overall brainwave activation and regional coherence. If such an accelerated psychedelic brain-state existed, one would expect to see sharp areas of occipital gamma coherence when viewing EEG output of people having intense visualizations. To demonstrate that this is an experimentally valid statement, I will offer the findings of DE Stuckey on his 2005 paper on the South American hallucinogen ayahuasca and EEG coherence in highly hallucinatory states:

"The most important findings were increases in global EEG coherence in the 36-44 Hz and 50-64 Hz frequency bands for both subjects. Widely distributed cortical hyper-coherence seems reasonable given the intense synesthesia during ayahuasca experiences. Other findings include increased modal EEG alpha frequency and global power decreases across the cortex in most frequency bands... We believe that finding increases in global gamma coherence during peak psychedelic experiences might contribute to the discussion of binding theory. Also, in light of recent research with gamma coherence during advanced meditative conditions, our findings might further the comparison of shamanic psychedelic practices with meditation." [14]

While this study demonstrates my point precisely, the science in this area is hardly conclusive. Depending of the type of EEG analysis performed, brainwave results from differing studies can have ambiguous results, like the following ayahuasca EEG study from Erik Hoffmann:

"Following three doses of the tea, the subjects showed strong and statistically significant increases of both EEG alpha (8-13Hz) and theta (4-8Hz) mean amplitudes compared to baseline while beta (13-20Hz) amplitudes were unchanged. The strongest increases of alpha activity were observed in the occipital lobes while alpha was unchanged in the frontal lobes. Theta amplitudes, on the other hand, were significantly increased in both occipital and frontal areas. Our data do not support previous findings of cortical activation with decreased alpha and increased beta activity caused by psychedelics" [18]

While these conflicting EEG studies can be confounding, all of these findings demonstrate that 5-HT_{2A} hallucinogens operate as phase-state drivers which can excite, disrupt, and resynchronize the intensity and global coherence of activity in the visual cortex. Slow wave theta binding increases in some cases, fast wave gamma binding increases in other cases. All cases tend to emphasize the increase or decrease in cohesion and synchrony between the frontal and visual cortex, demonstrating the strength of the bond between visual information, self awareness, and our subsequent perception and beliefs about reality.

EEG Coherence, Phase-State Drivers, and Optimized Circuit Synchrony in Cortical Loops

So far in this discussion we have described the psychedelic state as a series of sliding transitions between excited, destabilized, decoupled, and hyper-stabilized states. With so much going on in one pharmacological interaction it is easy to see why there are so many differing reactions to psychedelics; some glowing and some horrific. While the common wisdom in psychedelic circles is that "dose, set, and setting" create the difference between good trips and bad trips, I would like to offer a more subtle interpretation to this notion. Dose is obviously important for selecting how far along the extreme of psychedelic consciousness you wish to go, but set and setting are only important to the extent that they facilitate the smooth transitions

between the various multi-phasic brain states found within the trip.

What I am offering here is a model for measuring positive vs. negative psychedelic experiences based not on trip content but on the ease with which the subject can transition through excitation, destabilization, and decoupling to get to the all-important peak, or some similar hyper-coherent mind state associated with gnosis and mystical enlightenment, depending on what the subject seeks. The set, setting, and ritual of shamanic practice is thus primarily to help subjects and groups seamlessly navigate these transitory states, making sure internal brain rhythms destabilize gracefully, decouple, and re-cohere at optimized phase states for extended periods of time. This is typically done through ritual rhythmic activities such as drumming, clapping, chanting, music, and dance, all of which act as feedback pulse drivers for the hyper-coherent state. Without the environmental stimulus of rhythmic pulse drivers, or in the presence of conflicting pulse drivers, the subject is likely to become disoriented, panic, recede, get stuck in a loop, remain disoriented and panicked, and never properly re-cohere at an optimized phase-state. This is a perfect subjective description of a psychedelic “bummer”.

While much of this talk of phase state coherence is speculative and based on a handful of EEG studies, it should be noted that the plasticity of the psychedelic experience is a widely reported phenomenon. A psychedelic experience can morph from a low activity state to a high activity state based solely on environmental factors, and rhythmic drivers like music, chanting, or the repetition of small thoughts or “mantras” can kick the brain’s internal focus and imaging powers into overdrive. It should also be noted that most psychedelic hallucinations, open- and closed-eye, are accompanied by a kind of rapid rhythmic flickering or pulsation. The speed of this pulse – or “frame update” – directly corresponds to the intensity of hallucination seen, turning a slowly spinning spider web at low energy states into a rapidly swirling 3-D landscape at high energy states. Generally, the speed of the hallucinatory frame-rate corresponds directly to the primary rhythmic pulse driver, making fast-tempo trance music the preferred modern driver for achieving high-intensity visual hallucinations. Conversely, ambient music with no drums is the preferred soundtrack for producing dream-like visions that rise and morph slowly like smoke on the breeze. In both cases it is the music that drives visual synesthesia and eases the transition between excitation, decoupling, and subsequent re-synchronization.

HPPD, Chronic Disinhibition, and Maladaptive Neural Plasticity in Hebbian Complexes

While the multi-state model presented in this paper is merely speculation based on the best available data, it is plausible enough to consider what the short- and long-term adverse effects of this pharmacological action might be in subjects exposed to repeated high doses of psychedelic tryptamines. Besides the “bummer”, which we have already discussed, the initial assumption would be that if the subject eventually “winds-down” from the hyper-coherent state into a more normalized baseline state, that the effects of the drug should be 100% reversible. However, we know this is not always the case. The most documented long-term side-effect of psychedelic use is hallucinogen persisting perception disorder (HPPD), sometimes called post-hallucinogen perceptual disorder (PHPD), which is the persistence of low-level hallucinations described as closed eye geometric patterns and the “wiggling” or “drifting” of line and depth detail long after the drug has been metabolized, sometimes lasting weeks to months after a single psychedelic session. Another more mythical and less documented side-effect of psychedelic use is the “flashback”, or a spontaneous short-duration daydream of hallucinatory content while otherwise sober; like mini-psychedelic episode lasting no more than a few

seconds, similar to déjà-vu. Lesser studied adverse side-effects of frequent psychedelic use include the adoption of eccentricities in belief and behavior, occasionally to radical extremes. And in very rare cases psychedelics are the mitigating factor in pushing psychotic personalities over the edge, causing breaks from reality and persistent delusional and/or megalomaniacal ideation.

The conditions in the paragraph above are all well-known and documented adverse side-effects of psychedelic use, but until now there has been no underlying model of pharmacological action that attempts to account for the range of all these various abnormalities, beyond the ambiguous concession that psychedelics can sometimes “mess things up” in your head somehow. Yet I assert that that multi-state model of psychedelic action can shed light on all of these disorders, and can in turn lead to logical pathways for treatment and early intervention.

5-HT Mediated GABA inhibition and HPPD

In the case of HPPD it seems clear that persistent localized disinhibition in visual circuits is the logical culprit; technically described as the loss of the ability to hold sharp contrast intensity in the visual field. This is the very definition of destabilization; lateral inhibition has been overridden to the point of creating infinite perceptual ambiguity. While the science in this area remains unresolved, a likely target for this interaction would be in persistent recurrent feedback offsetting GABA_B inhibitory postsynaptic potentials (IPSPs) at the lateral-inhibitory synapse. From a paper on the subject by Zhengwei Shao and Andreas Burkhalter:

“Feedback stimuli of a wide range of intensities increased the rate of ongoing neuronal firing. Thus, when forward and feedback inputs are simultaneously active, feedback inputs may provide late polysynaptic excitation that can offset slow IPSPs evoked by forward inputs and in turn may promote recurrent excitation through local intracolumnar circuits. This may provide a mechanism by which feedback inputs from higher cortical areas can amplify afferent signals in lower areas.”

What is being suggested here is that rhythmic top-down feedback can override localized tonic inhibition and amplify recurrent feedback of sensory signal. Not only does this top-down model of recurrent excitation overriding localized tonic inhibition fit with the multi-state model presented here, it also provides a pharmacological basis for describing the perceptual symptoms of HPPD. If the localized IPSPs in the central columnar layers can be offset by simultaneous polysynaptic excitation from both forward and feedback inputs, any drug which strengthens the pulse coupling between forward-feedback polysynaptic recurrent pathways could override the capacity for slow GABA_B IPSPs to inhibit the recurrent impulse.

The persistence of this effect after intoxication wears off may be due to purely neurotoxic means – such as the corruption of 5-HT mediated inhibitory interneurons by cellular damage or stress-induced down-regulation at 5-HT_{2A} uptake sites – or in chronic HPPD cases it may be the result of psychedelic-induced neuroplasticity reinforcing late polysynaptic excitation of intracolumnar circuits.

Pulse-Driven Phase Coupling and Flashbacks

While the psychedelic flashback itself is an elusive beast, we know enough about it to make some assumptions based on the multi-state model presented here. Like déjà vu, the flashback is the instinctual subconscious recognition of a pattern or form which evokes hallucination or the hyper-coherent state of psychedelic consciousness. Assuming that various states of

consciousness can be construed in terms of the pulse-driven couplings of various brain areas, it can be said that psychedelics “introduce” the brain to novel patterns of pulse-driven couplings, creating wholly novel and unique brain states. Once familiar with these new “psychedelic” brain patterns anything that evokes these patterns is instantly recognized as “psychedelic”, thus creating a memory or flashback of that unique archetypal state. The hyper-coherent phase-state created by psychedelics does not happen spontaneously in human consciousness (though the argument could be made in the case of sleep deprivation and extreme manic-psychosis), but the memory of that induced state may be enough to invoke a slight shift in waking phase state close enough to recall some small echo of the experience.

Persistent Psychedelic-Induced Delusional Psychosis

There's no doubt that the worst-case-scenario of a psychedelic experiment is that the subject never comes back the same, and is somehow irreparably changed or damaged by the process. While it is widely recognized that this is a very real possibility, no good explanation for this phenomena is ever offered other than “pre-existing psychotic tendencies”. While this explanation may be accurate it tends to pin the blame on the victim and never attempts to describe the mechanics underlying the catalyst for such a dramatic change. It is sadly lacking as workable theories go.

Within the multi-state model of psychedelic action presented here it seems obvious that there are multiple pathways through which an individual may induce a kind of permanent psychosis or delusional belief system that persists long after the drug is metabolized. The first and most obvious conclusion is that the subject's pre-existing psyche was simply fragile, and the psychic trauma of the psychedelic experience blew a gasket in the network somewhere. While this is convenient it doesn't answer the hard questions of what differentiates a robust psyche from a fragile psyche, and what actually “breaks” during the process of psychedelic activation. It could be argued that persistent overloading, decoupling, and “re-booting” of the entire cortex puts a strain on the network that, over time, degrades the brain's ability to retain global cohesion in a normal waking state. This could be defined as a kind of network burnout resulting in scattered and un-focused personality disorders. If network burnout were the culprit, one would expect the results to be reversible through sustained abstinence, but since there are few studies in this area these speculations remain unresolved.

But there is another more complex piece to this puzzle that cannot be entirely overlooked, and that is the notion that persistent psychedelic delusion is not due to network burnout or damage due to neurotoxicity, but is instead due to runaway synaptic growth along eccentric logic and memory pathways, similar to what would be seen in cult deprogramming and brainwashing subjects.

While the premise of psychedelic neural damage is politically convenient for the anti-drug lobby, the argument for maladaptive psychedelic neural growth is a much trickier issue from every angle. The sinister use of psychedelics in brainwashing and cult deprogramming has been understood for many decades now, but nowhere is it asserted that psychedelics can promote plasticity and new synaptic growth along logic and memory pathways. The efficacy of psychedelics as brainwashing, mind control, or cult-induction tools may come precisely from their unique ability to decouple the cortex and retune it with novel pathways. In psychedelic therapy the process of undoing maladaptive pathways is called “catharsis”; the process of wiring novel pathways out of the psychedelic experience is called “integration”. In psychedelic literature the process of doing this to the self is called “metaprogramming”. In each of these instances psychedelics are used to remove previous associations and re-train new beliefs and

behaviors. If we are to take for granted that psychedelics facilitate this process of synaptic plasticity, then it must be presumed that this very process can be used to imprint and reinforce positive as well as delusional and maladaptive belief systems over time.

In the case of maladaptive psychedelic programming, one would expect to see the subject crafting self-referential occult belief systems based on ambiguous or archetypal symbols over a period of many months, weeks, or years. These occult belief systems would become more complex over time, relying on a hyper-articulated network of connections between language and symbol systems, thus creating eccentric logic pathways that grow so tangentially elaborate they eventually eclipse common rationality. A person suffering from this syndrome may also exhibit messianic or megalomaniacal tendencies, such as the belief that their occult system was derived from divine origin, along with the urgent need to spread a paradoxical prophecy of doom and transcendence. This syndrome is not symptomatic of neural damage or breakage, it is symptomatic of wholly unique logic pathways forged through obsessive self-referential feedback ideation, facilitated and reinforced through repeated high-dose application of selective 5-HT_{2A} agonists.

In Conclusion

Psychedelics represent many things to many people. They are both the worst demon of the anti-drug movement and the highest-angel of the pro-drug movement. This is not without cause. If we are to take the multi-state model seriously and view psychedelics as gateways to open-ended mind-states based solely on dose-range and environmental rhythmic modulators then it is implicit that these chemicals are utilitarian in achieving recreational, mystical, and plasticity-induced neural programming results in almost all human subjects. The fact that these molecules occur in nature is a testament to the fundamental chemical similarities of all organic neural logic pathways as well as the open-ended mechanical capacities of neural networks and thus our own imaginations. By embracing the multi-state model of psychedelic action we must recognize as a species that these chemicals are essential to the growth and evolution of our neural hardware, but can paradoxically induce psychosis and reinforce delusional belief systems when used imprudently or to excess.

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