Neurological Foundations of Hallucinogenic Experiences:

Long-Term Effects & Phenomenological Insights

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Acknowledgement: Nick M. Heinz, San Francisco State University

Abstract

Hallucinogenic substances uniquely facilitate the study of consciousness by chemically inducing specific phenomenological experiences, such as ego dissolution, enabling researchers to trace neurobiological pathways from molecular interactions to profound, often long-term, changes in perception, behavior, and self-awareness. These long term changes are especially apparent in the reduction of relapse for people addicted to alcohol and heroin[1].

This presentation explores how these substances, through their reliable interactions with key neurobiological mechanisms, could evoke acute phenomenological experiences and lead to persistent alterations in cognition and mood.

Utilizing a blend of neuroimaging data, biochemical pathways, and behavioral outcomes, we investigate the mechanisms underlying persistent modifications in neural plasticity and memory systems. We propose that fast-forming functional filopodial connections may account for some of the long-term changes and the short-term fluidity of thought that hallucinogens are known for. We will cover short term and long term neuro-plastic changes and short term and long term cognitive changes induced by classical hallucinogens, principally Lysergic acid diethylamide, commonly known as LSD. This study further investigates how these alterations correlate with significant changes in cognition, thereby providing a mechanistic understanding of the enduring impacts of psychedelic experiences.

Through this neurobiological lens, we aim to help bridge the gap between phenomenological data and their underlying physical processes, enhancing our understanding of how psychedelic substances reshape cognitive and perceptual processes.

Key Concepts & Background

Hallucinogenic Substances and Consciousness

Phenomenological Experiences: Hallucinogens like LSD can chemically induce specific experiences such as ego dissolution, enabling researchers to map neurobiological pathways from molecular interactions to profound changes in perception, behavior, and self-awareness.

Known Mechanisms of Action

5-HT_{2A} Receptor Activation: LSD and other hallucinogens activate 5-HT_{2A} receptors, which play a critical role in both short-term and long-term neural plasticity.
Short-Term Effects: Activation leads to short-term potentiation by increasing neurotransmitter release and enhancing action potential strength.
Long-Term Effects: Promotes dendritic growth and spinogenesis, resulting in increased neural connectivity.

Ego Dissolution

Definition: Ego dissolution is an experience where individuals lose the sense of self and identify with other people, objects, or systems. It is characterized by the feeling of "being one with everything" and can have positive or negative valence.
Dose-Dependent: LSD induces ego dissolution in a dose-dependent manner, continuing to increase with higher doses up to 200 micrograms.
Significance: This experience is often described as profound and significant, influencing long-term changes in cognition and behavior.

Long-Term Cognitive Changes

Addiction Reduction: LSD has been shown to significantly reduce relapse rates in alcohol and heroin addiction, with effects lasting several months to over a year.
Anxiety and Depression: LSD can lead to significant reductions in anxiety and depressive symptoms, particularly correlated with higher ego-dissolution experiences.

Short-Term Neural Plasticity

Mechanisms: LSD activates 5-HT_{2A} receptors, leading to short-term neural plasticity by increasing the release of neurotransmitters and enhancing action potentials.
Experimental Evidence: Studies demonstrate the necessity of 5-HT_{2A} receptors for hallucinogen-induced behaviors, underscoring their critical role.

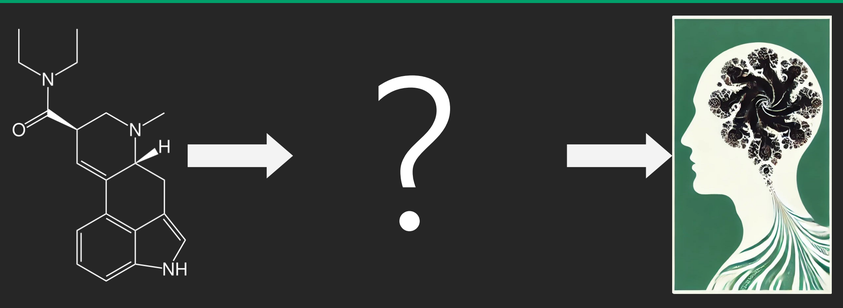
Long-Term Neural Plasticity

Dendritic Growth: LSD promotes significant dendritic growth and increases in spinogenesis, mediated primarily through 5-HT_{2A} receptors.
Inhibition Studies: Blocking 5-HT_{2A} receptors eliminates LSD-induced neurogenesis and spinogenesis, highlighting their essential role.

Proposed Mechanisms for Short & Long-Term Effects

Filopodial Connections: Rapid growth of functional filopodial connections between neural ensembles is proposed to mediate both short-term experiences (like ego dissolution) and long-term cognitive changes.
Short-Term: Creation of functional connections via filopodia and serotonergic short-term potentiation leads to ego dissolution by bridging signals in the anterior temporal lobe.
Long-Term: Persistent filopodial connections disrupt entrenched neural propagational patterns, allowing new cognitive patterns to form, reducing symptoms of addiction, OCD, and PTSD.

Motivating Question



We know that a chemical compound, Lysergic acid diethylamide (LSD), can reliably lead to specific modulations of perceptive objects and states. Moreover, it is able to elicit, across individuals, cultures, and various contexts, once central basic precept, which is the feeling of "oneness" with the universe and/or the loss of self generally.

As such LSD is a prime target for the explanation of a phenomenological state, because it seems to have to do with the modulation of a fundamental, structural, process in the mind.

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Long-Term Effects & Mechanisms

Established Long-Term Effects of LSD Exposure

A dramatic reduction in relapse from addictive drugs like alcohol and heroin is one of the more long lasting effects of LSD. Studies on addiction have found beneficial effects on relapse negation when compared with controls lasting for at least 3 months in most studies, and beneficial effects in some but not all studies lasting up to 12-18 months until relapse for alcohol[4]. Similarly, relapse in heroin use against controls were significantly lower for LSD treated participants than controls[4].

There is a somewhat similar effect seen with anxiety, with anxiolytic (anti-anxiety) effects being most pronounced at 2 weeks after a secondary dose of LSD and persisting to at least 16 weeks after said dose. In the same study, significant reductions in depressive symptoms were also seen, and followed a similar time course. Interestingly, higher measures of ego-dissolution correlated with more robust anxiolytic effects in patients with anxiety disorders[5].

Established Long-Term Plastic Effects

Research which monitored neural dendritic reactions to LSD administration demonstrated a marked increase in dendritic arbor density in LSD treated neurons when compared to the same neuron pre-LSD administration and controls. The inactivation of 5-HT_{2A} receptor function through a selective antagonist led to the complete extinction of the LSD precipitated increases in neurogenesis and spinogenesis[9], implying that LSD primarily exerts its influence on dendritic growth and plasticity through 5-HT_{2A} mediated processes. This is an important consideration since 5-HT is the protein receptor which locks on to LSD and is subsequently left tonically open, until the cell lyses the LSD & 5-HT_{2A} complex apart[7].

Short-Term Effects & Mechanisms

The Short-Term Changes Induced by LSD: Ego Dissolution

There are many short-term effects of LSD, here we concern ourselves primarily with ego dissolution or ego death, defined simply as an experience of identification with other sets of people, objects and/or systems, with or without an identification with the self broadly defined. At its most severe, this experience has been described as identifying with everything. In standardized questionaries, ego dissolution corresponds roughly to ratings of both "Oceanic Boundlessness" and "Anxious Ego-Dissolution", with the former indicating a positive valence to the experience of ego dissolution, and the latter indicating a negative valence[2]. This experience is usually described as being of great significance by those who experience it, and variably described as being a profoundly positive or profoundly negative event.

LSD reliably elicits ego dissolution at high doses. Interestingly, while most effects of LSD reach a ceiling at 100 µg, ego dissolution continues a dose dependent increase to at least 200 µg [3]. Moreover, while peak report of ego death constituent experiences is at around 3 hours, the constituent experience scores begin to rise at less than one hour[3].

Established Short-Term Plastic Effects

5-HT_{2A} is a neurotransmitter receptor which normally accepts serotonin and, among other processes, mediates short term potentiation. It, along with several other 5-HT receptors (serotonin receptors) are activated by LSD. LSD administration leads to the non-transient activation of 5-HT receptors by changing its morphology, so when the receptor takes in LSD, it continues to operate as if it had bound serotonin until it is removed by the cell from the cell membrane[7]. 5-HT_{2A} leads to short term potentiation by moving reserve vesicles at presynaptic neurons towards the synapse and allowing them to be dumped, leading to an increase in whatever neurotransmitters that neuron is responsible for[7]. Normally, serotonin from a serotonergic neuron precipitates that process in the downstream, or post-synaptic, neuron.

Through a complex set of signaling cascades, 5-HT_{2A} also leads to increased strength of action potentials. So you get more neurotransmitters sent out, and a stronger action potential going downstream[6].

Short-term effects of LSD as a whole seem to be mediated by 5-HT_{2A}. An experiment with mice without the receptor demonstrated no hallucinogen –induced head shaking. When the same mice had the 5-HT_{2A} receptor selectively restored in cortical pyramidal neurons, the hallucinogen-induced head shaking was restored[8].

Proposed Long-Term Effects & Mechanisms

Proposed Short & Long-Term Plastic Effects

This poster proposes that one of the principal processes which leads to hallucinogen precipitated long-term changes in behavior and cognition, as well as short-term experiences like ego death, is the increase in functional connectivity driven by the rapid growth of functional filopodial connections between neural ensembles.

The long-term changes in behavior and cognition are proposed to be attributable to the creation, retention, and maturation of filopodial connections created in the span of 30 minutes to a few hours after LSD administration. We posit that the combination of neural ensembles firing and rapid growth of neurites leads to the maturation of what would otherwise be transient connections. These connections lead to the disruption of neural propagational patterns that are deeply entrenched, by increasing the number of directions the propagation can go towards. These changes in the direction of neural propagations, corresponding to changes in cognitive processes, translate into the reduction of highly conserved thoughts and behaviors.

These highly conserved cognitive and behavioral patterns can range from those underlying compulsive drinking, to those underlying Obsessive Compulsive Disorder or PTSD. If it has to do with entrenched behavioral or thought patterns, the increase in neural connectivity is going to allow for the "escape" of cognitive propagations from the entrenched propagational pathways corresponding to entrenched thought patterns, and can subsequently lead to the development of newly developed and subsequently conserved patterns, which may be less deleterious.

In relation to its effects on depression, the same increase in neural connectivity could lead to LSD induced heightened activation of neural systems important to perception, such as the striatum. The administration of LSD leads to reduced depressive symptoms which last for several months, but are not retained for past a year or so[4]. Since LSD can affect the striatum, due to the significant presence of 5-HT_{2A} receptors there, this may be a significant aspect of LSD's anti-depressive effects.

Proposed Short & Long-Term Plastic Effects: Ego Dissolution

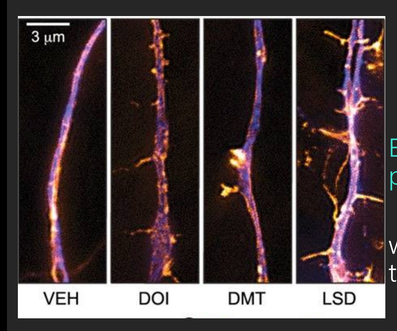
We posit that the particular experience of ego dissolution is a consequence of both the creation of new functional connections via filopodia, and serotonergic short term potentiation leading to the bridging of signals in the anterior temporal lobe representational hub between the self-representation and other representations. This concurrent activation of multiple cognitive ensembles is purported here to be the neural process underlying ego dissolution. We assert that as the propagational patterns normally contained in the self representation "leak out" of the entrenched pathway, it becomes difficult for the representational system to attribute sensory and relational information solely with the self-representation.

In short, because of the added functional connectivity between the self representational ensembles and those of other objects and people, the cognitive representational system loses the ability to compute just the self, without other representations also being activated. We further propose that this pattern of activation is not retained past a few hours because the short-term serotonergic potentiation effects attributable to LSD exposure die down after the removal of LSD-5-HT_{2A} receptor complexes over the same span of a few hours.

Owing to the connectivity being a significant factor in our view, we predict that in populations like those with drug dependencies and obsessive compulsive disorders, will see a dose dependent decrease in the undesirable behavioral and cognitive patterns. Moreover, we predict that, when tested, the degree of ego-dissolution induced by LSD will positively correlate with the reduction in symptoms, in a relatively invariant way across individuals, as ego-dissolution can be used as a proxy for the degree of connectivity established by the administration of LSD.

Finally, we expect that these LSD mediated changes in connectivity will also correlate to changes in conscious processing, especially due to the changes in dopamine at the striatum, the increased connectivity across the cortex, but mainly at the PFC and ATL, and the overall disruption of the cortico-striato-thalamo-cortico neural circuit, which has been proposed to be heavily involved with subjective time perception [10].

LSD Mediated Dendritic Growth



Effect of Hallucinogens on Neuron Morphology

VEH= Vehicle, or rather control. Here we see the dendritic growth occurring after 24 hours of exposure to LSD in-vitro[9].

Conclusion

Discussion

The alterations in neural connectivity and plasticity mediated by LSD result in significant cognitive and behavioral changes, which are pivotal in understanding how psychedelics can reshape entrenched neural pathways and offer new therapeutic avenues.

LSD's ability to induce ego dissolution and increase neural arbor density in a dose-dependent manner has significant implications for therapeutic use, particularly in treating conditions like addiction, anxiety, and depression.

While the risk of psychological harm is minimal, and the risk for physical harm nearly non-existent for psychedelic therapy, this framework could allow us to use hallucinogens in a more targeted manner. For instance, for depressive symptoms, it may be the case that one need not be conscious to receive the anti-depressive benefits of LSD. On the other hand, conditions like PTSD and OCD may require more therapeutic guidance, as entraining the mind to be able to take itself out of a given dynamic may be necessary for hallucinogen assisted therapy to have its intended effect.

I believe that this account of LSD function presents a first draft framework by which the field can begin bridging phenomenological facts with their neurobiological mechanisms. As such, this research has attempted to set a path for building our understanding of how psychedelics affect the brain and consciousness, paving the way for future studies and therapeutic applications.

Future Directions

Research demonstrating that 5-HT2A mediates dopamine in the VTA, PFC, and striatum, inducing increases in dopamine, has interesting implications for the phenomenological report that time is dilated to the extreme when LSD is administered at high doses, as those areas have been purported to be important to time-consciousness. Future work will work to integrate these findings with a model of time-consciousness which involves those brain areas, with particular emphasis on understanding the LSD precipitated changes in striatal population code progression.