

# Hallucinogens

Drugs that produce unusual sensory, perceptual and cognitive distortions



Derived from plants (mushrooms, cacti); but some are synthetic. Include: **mescaline, psilocin, DMT, LSD**

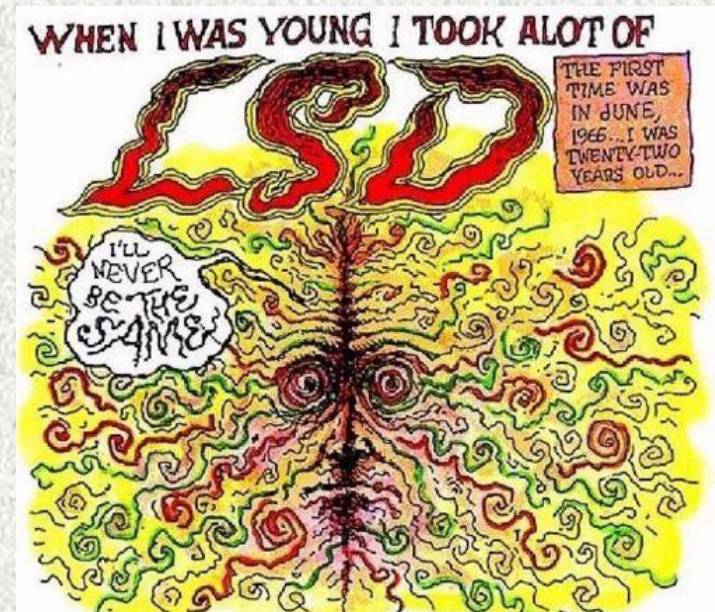
# Depictions of the effects of hallucinogens



**Yan Dargent** "Le rêve d'un éthérés" A depiction of ether-induced hallucinations 1865



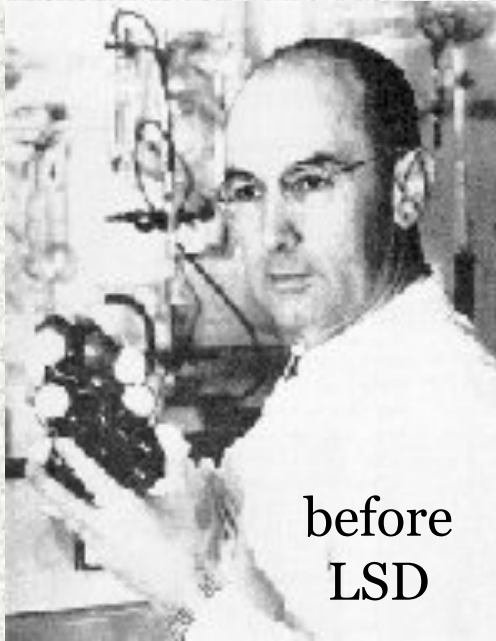
**Viktor Oliva** "The absinthe drinker" 1901



**Robert Crumb** "LSD"

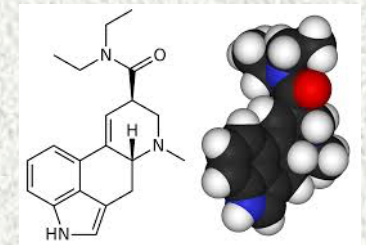
# LSD

A synthetic **ergot** derivative synthesized by **Albert Hoffman** in 1938 (LSD-25)



before  
LSD

after LSD!



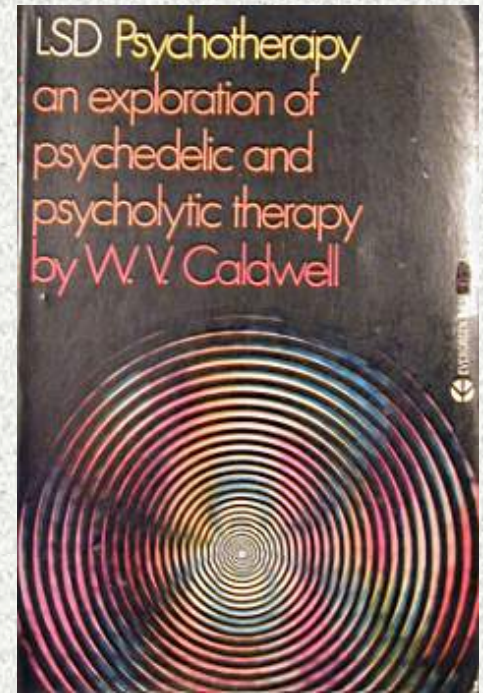
ergot fungus

Some derivatives toxic; some clinically useful  
LSD re-examined in 1943; Hoffman ingested it (by accident) and took an unusual trip!  
**LSD is a very potent drug...**

# Early applications

LSD initially available to psychiatrists and medical researchers (1940 - 1962)

**Psycholytic therapy:** Popular in Europe; LSD in psychotherapy to release repressed memories



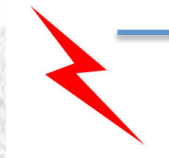
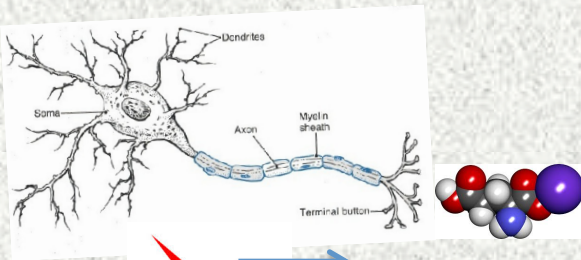
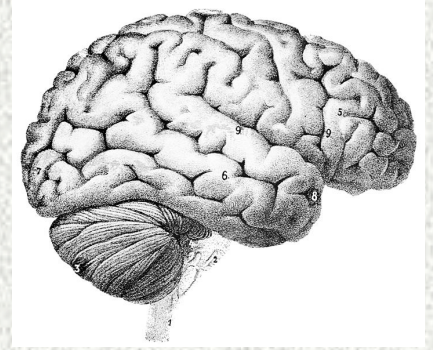
**Psychedelic therapy:** Popular in U.S.; LSD in high doses for “spiritual” shock



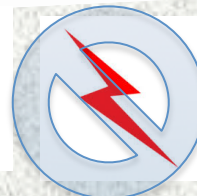
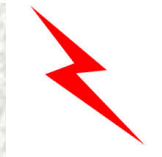
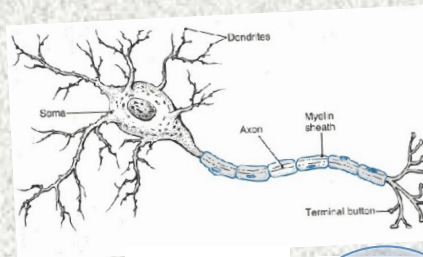
**MK-ULTRA:** 1950's CIA program, secret LSD administration to U.S. citizens; [British testing too](#)

# Your brain: made of cells

- Neurons
- Neurons carry *electrical* messages
- Neurons connect *chemically* across synapses
- Neurotransmitters

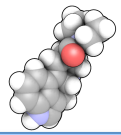


SYNAPSE

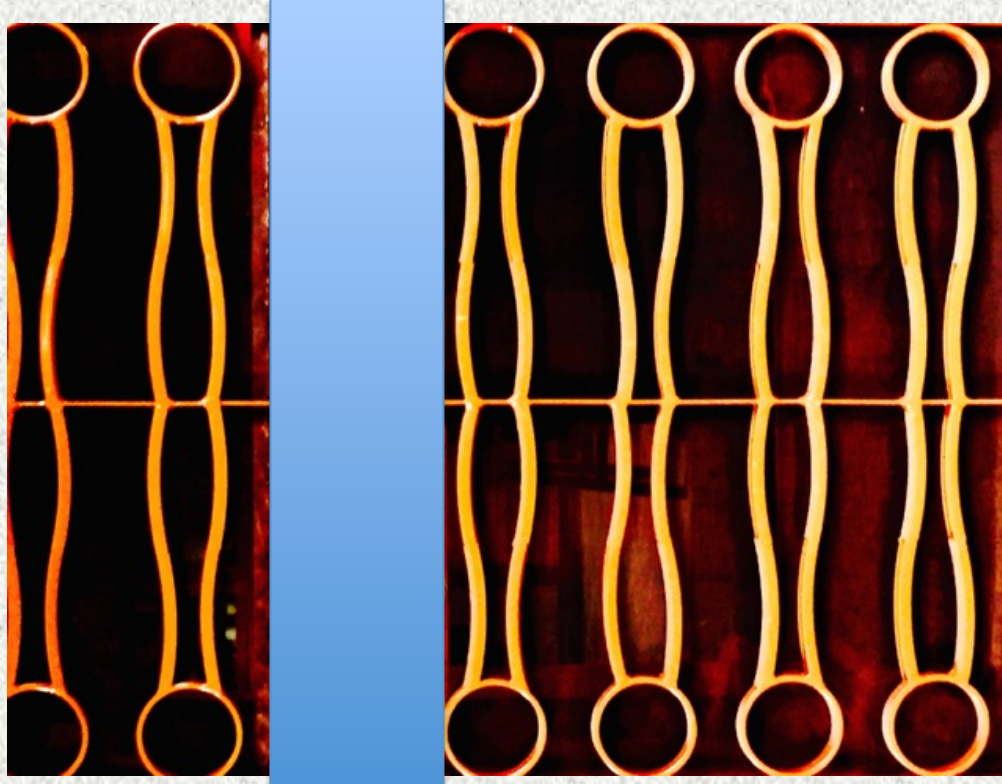


# All cells have membranes

Neurotransmitter  
or drug



Outside cells, including neurons



Many drugs, including hallucinogens, cannot get through, but instead act at RECEPTORS to affect neuron function...

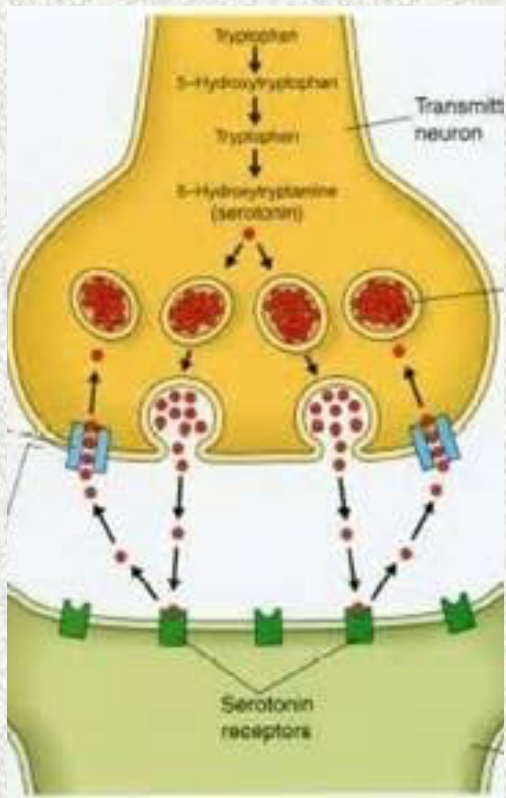
Drugs like LSD attach (or “bind”) to receptors, changing the activity of affected neurons...

Inside cells

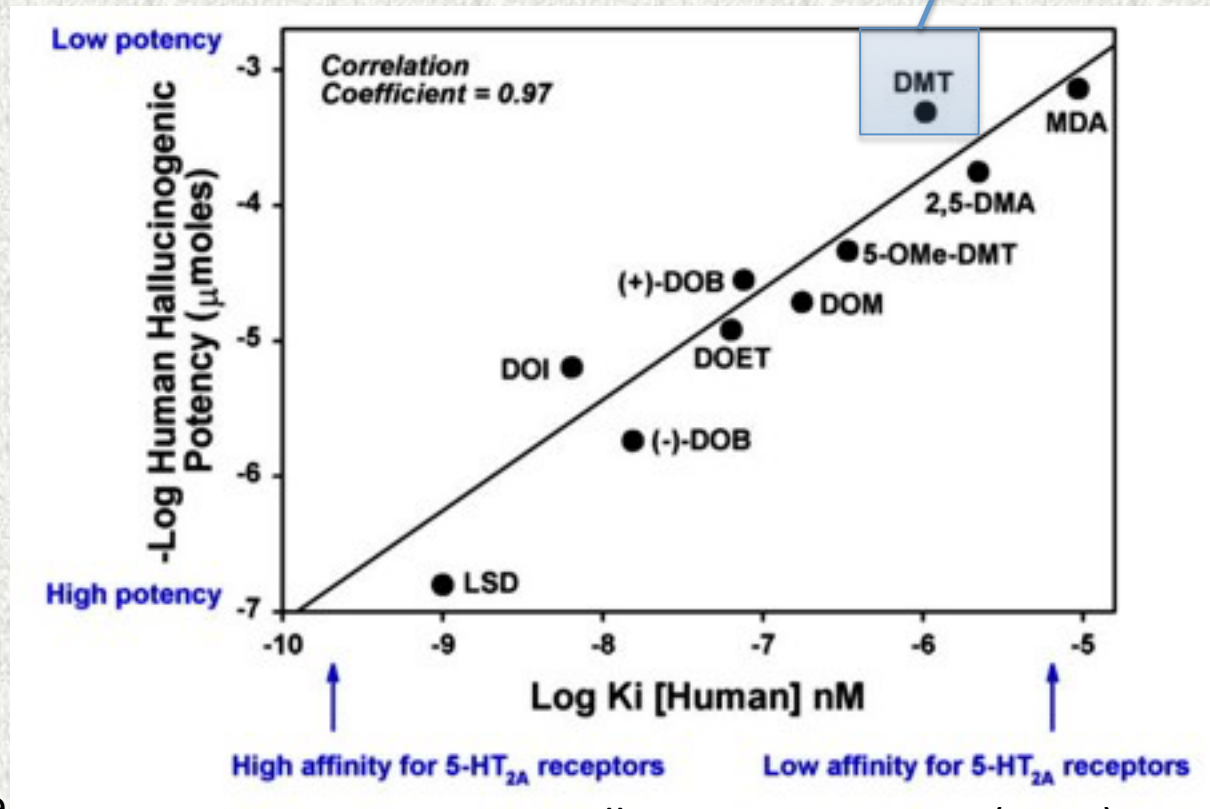
↑  
RECEPTORS: “Protein machines”

# MOST hallucinogens act at ONE type of SEROTONIN receptor (5-HT<sub>2A</sub>)

5-HT<sub>1A</sub>  
([Shen, 2010](#))



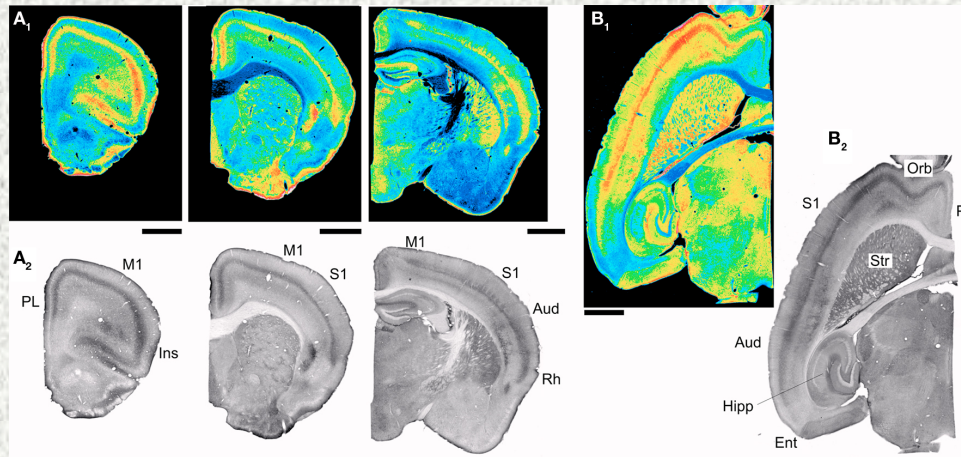
5-HT<sub>2C</sub> action plays a role in modulatory control of effects (Winter, 1999)



Wenjie Xiao, William E. Fantegrossi (2006)

**Potency linked directly to hallucinogenic effects**

# Where are these receptors?



Virginia Cornea-Hébert (1999)

- Neocortex  
– Layer V
- Olfactory cortex
- Hippocampus
- Basal ganglia
- Thalamus
- Cerebellum
- Brainstem
- Spinal cord

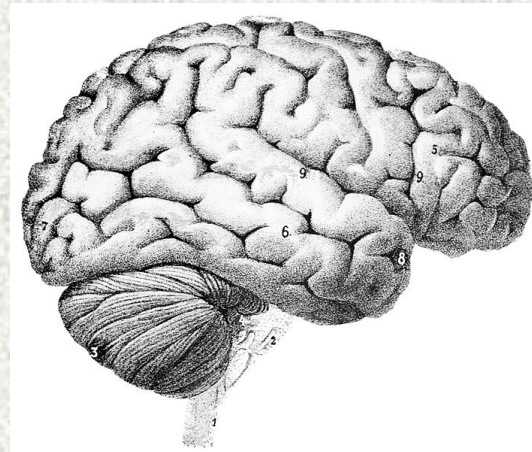
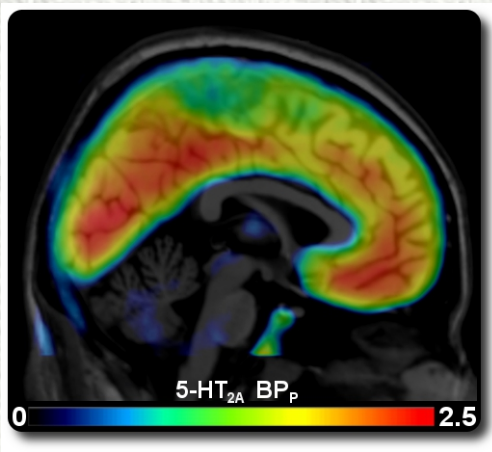


IMAGE SOURCE: [5-HT<sub>2A</sub> distribution map \(PET\); Medical University of Vienna](#)



# Changes in perception

“If the doors of perception were cleansed, everything would appear to man as it is, infinite” - William Blake

“The legs, for example, of that chair - how miraculous their tubularity, how supernatural their polished smoothness”  
- Aldous Huxley, “The Doors of Perception” (1954)

“I looked around me and noticed details of physiognomy that had never struck me before. Each pore in my companion’s skin was now visible...”  
- Solomon Snyder, “Drugs and the Brain”

“I clapped my hands and saw sound waves passing before my eyes”  
- Solomon Snyder, “Drugs and the Brain”

Hallucinogens  
affect the “gating”  
of sensory input

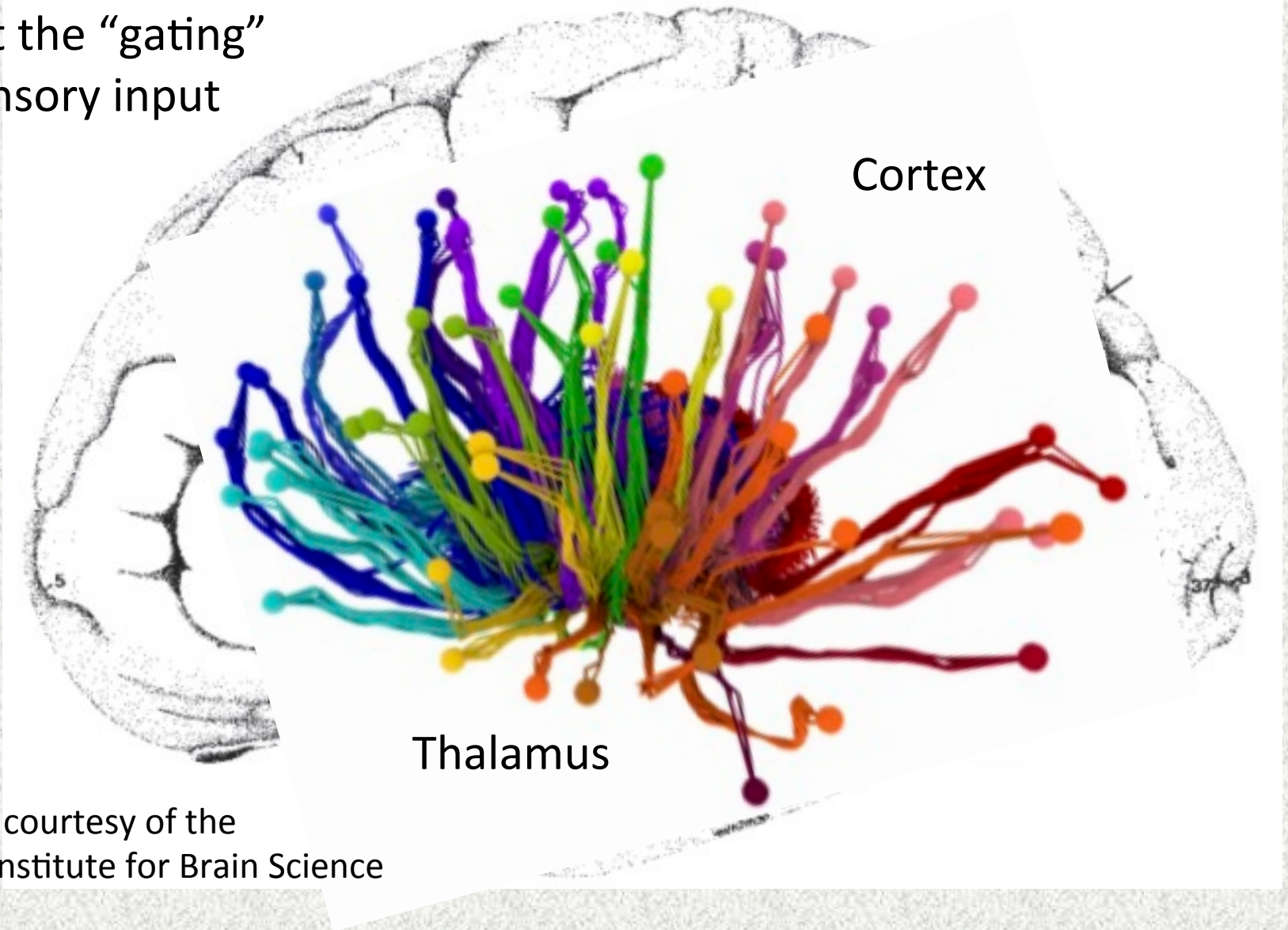
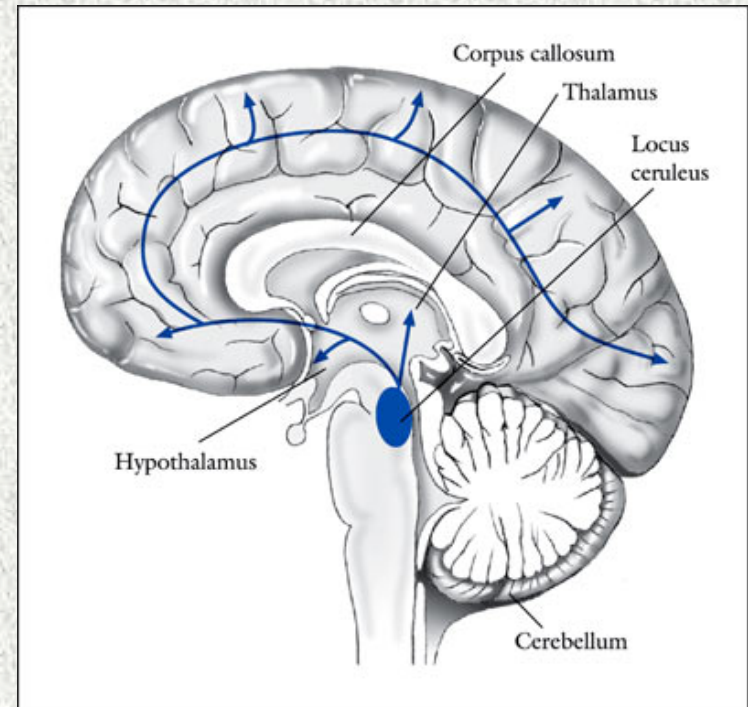


Image courtesy of the  
Allen Institute for Brain Science

# Hallucinogens Enhance Sensory Responses in the Locus Coeruleus via 5-HT<sub>2A</sub> Receptors

*Ordinary  
stimuli become  
extraordinary*



“...it is of interest that the systemic administration of LSD, mescaline, or other psychedelic hallucinogens in rats, although decreasing spontaneous activity, produces a paradoxical facilitation of the activation of LC neurons by sensory stimuli...”  
(Aghajanian 1980; Rasmussen & Aghajanian 1986)

# What else do hallucinogens do?

Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin, Carhart-Harris et al, PNAS (2011)

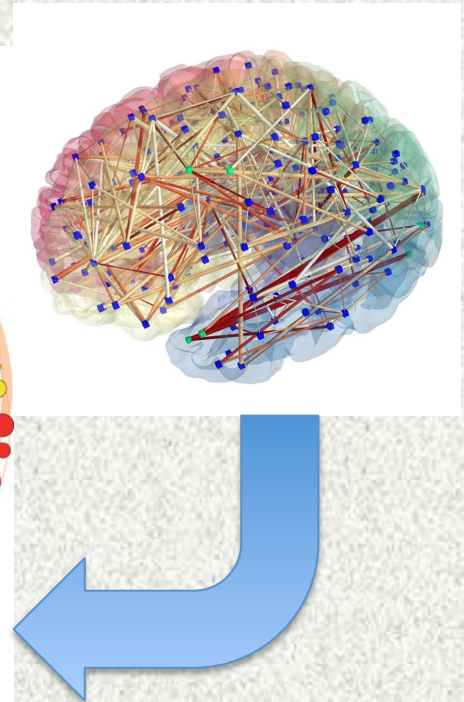
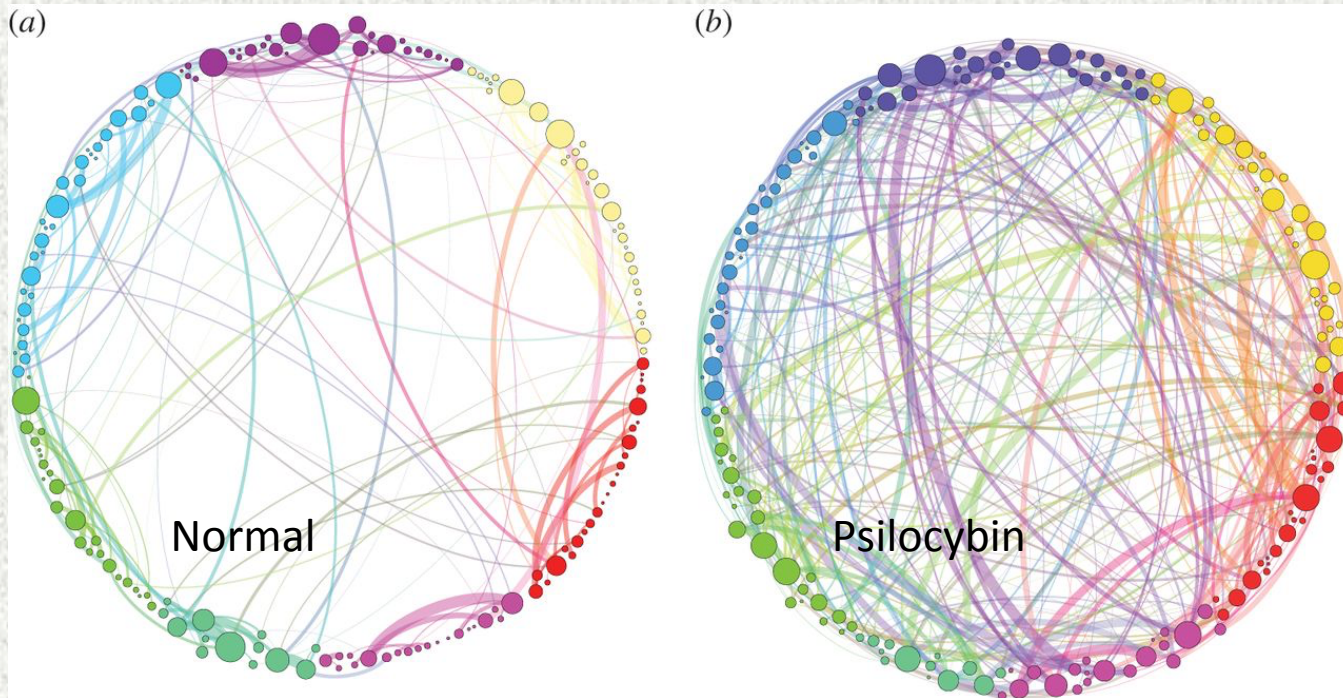
Psychedelic drugs have a long history of use in healing ceremonies, but despite renewed interest in their therapeutic potential, we continue to know very little about how they work in the brain. Here we used psilocybin, a classic psychedelic found in magic mushrooms, and fMRI to capture the transition from normal waking consciousness to the psychedelic state.

Profound changes in consciousness were observed after psilocybin, but surprisingly, **only decreases in cerebral blood flow were seen, maximal in hub regions, such as thalamus and anterior and posterior cingulate cortex (ACC and PCC)**. Decreased activity in ACC/medial prefrontal cortex (mPFC) was a consistent finding and the magnitude of this decrease predicted the intensity of the subjective effects. Psilocybin caused a **significant decrease in the coupling between the mPFC and PCC**.

**These results strongly imply that the subjective effects of psychedelic drugs are caused by decreased activity and connectivity in the brain's key connector hubs, enabling a state of unconstrained cognition.**

# Greater functional connectivity

Homological scaffolds of brain functional networks, G. Petri, et al (2014)



“there is an increased integration between cortical regions in the psilocybin state... One possible by-product of this greater communication across the whole brain is the phenomenon of synaesthesia which is often reported in conjunction with the psychedelic state...”



*Autumnal Fantasy*  
Charles Burchfield (1916-1944)

# Changes in sense of “self”

“Worse than the demonic transformations of the outer world were the alterations that I perceived in myself...Every exertion of my will, every attempt to put an end to the dissolution of my ego, seemed to be wasted effort.”

-Albert Hoffman (1948)

“The fear, as I analyze it in retrospect, was of being overwhelmed, of disintegrating under a pressure of reality greater than a mind, accustomed to living in a cozy world of symbols, could possibly bear.”

- Aldous Huxley, “The Doors of Perception” (1954)

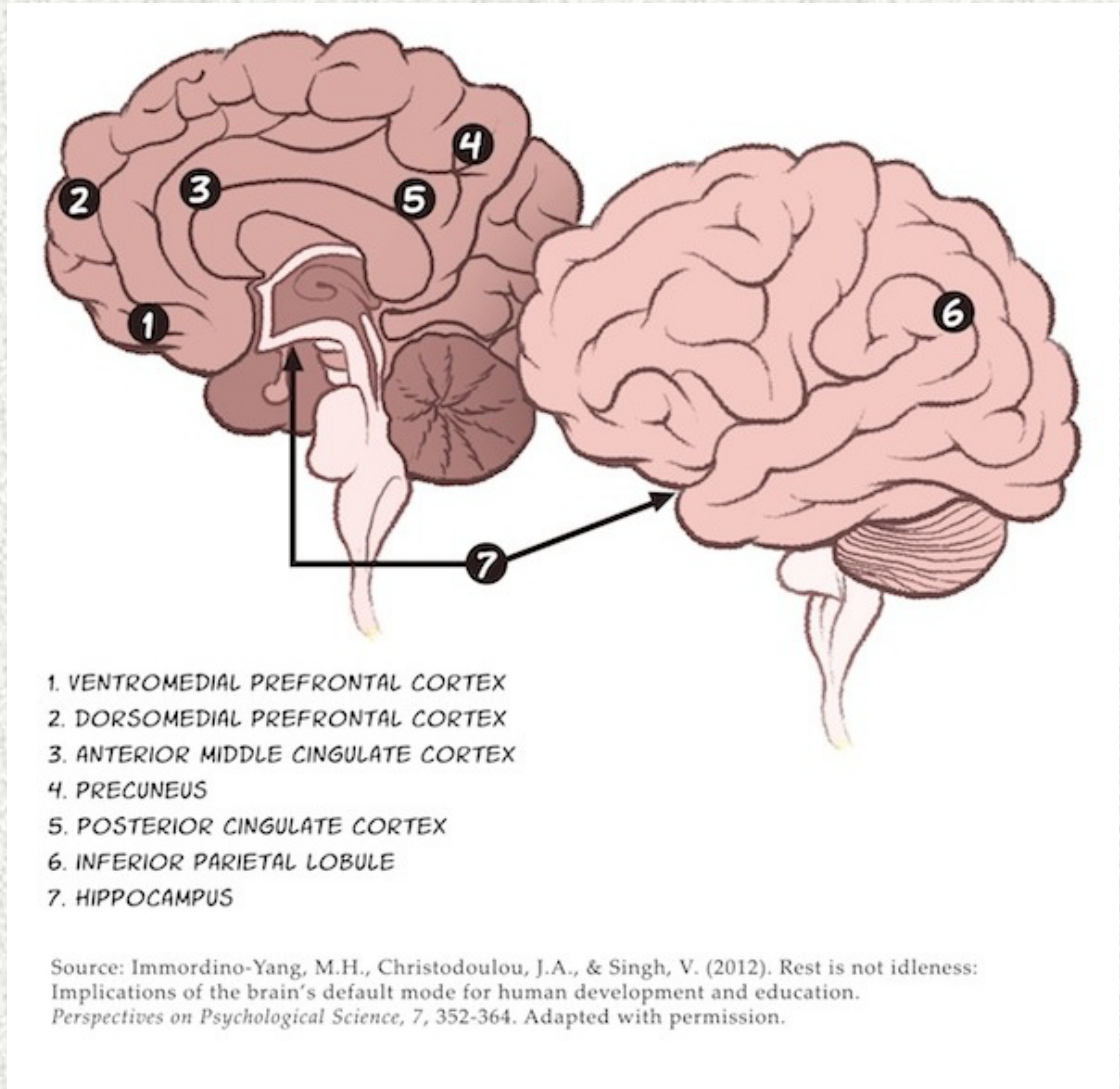
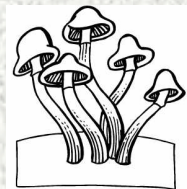
“Who am I?”

- Solomon Snyder, “Drugs and the Brain”

# “Default mode” network

Critical for...  
Self-reflection  
Self awareness  
Rumination

*Decreased activity*  
on hallucinogens  
(psilocybin)



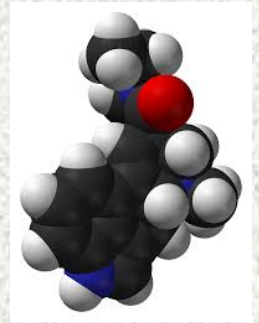
1. VENTROMEDIAL PREFRONTAL CORTEX
2. DORSOMEDIAL PREFRONTAL CORTEX
3. ANTERIOR MIDDLE CINGULATE CORTEX
4. PRECUNEUS
5. POSTERIOR CINGULATE CORTEX
6. INFERIOR PARIETAL LOBULE
7. HIPPOCAMPUS

Source: Immordino-Yang, M.H., Christodoulou, J.A., & Singh, V. (2012). Rest is not idleness: Implications of the brain's default mode for human development and education. *Perspectives on Psychological Science*, 7, 352-364. Adapted with permission.

Carhart-Harris et al, PNAS (2011)



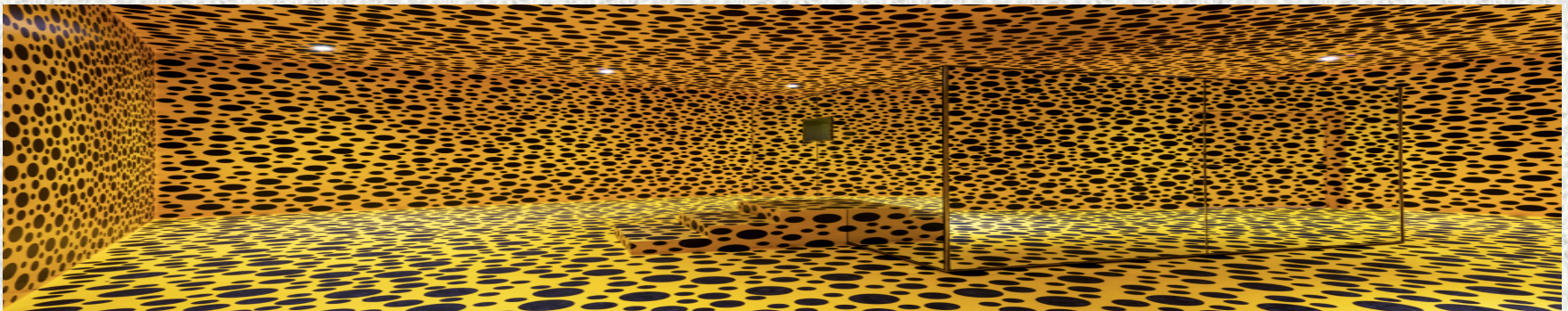
# Long-lasting subjective effects of LSD in normal subjects, Yasmin Schmid & Matthias E. Liechti (2017)



## *Abstract*

**Rationale** Lysergic acid diethylamide (LSD) and other serotonergic hallucinogens can induce profound alterations of consciousness and mystical-type experiences\*, with reportedly long-lasting effects on subjective well-being and personality.

- \* Perceptual changes and changes in the sense of “self”
- ✓ Re-orientation to a more novel, salient outside world?
- ✓ Reduced internal rumination; changed conception of “self”?



# Methods

Schmid & Liechti (2017)

**We investigated the lasting effects of a single dose of LSD (200 µg)...administered in a lab setting in 16 healthy participants.**

“LSD in oral doses of more than 100 µg produces vivid psychosensory changes, including increased sensory perception, illusionary changes of perceived objects, synesthesia, and enhanced mental imagery. Affectivity is intensified. Thoughts are accelerated, with their scope broadened including new associations and modified interpretation and meanings of relationships and objects. Ego identification is usually weakened.” -From [Gasser et al \(2014\)](#)



***Subjective questionnaires before, 1, 12 months after***

Persisting Effects Questionnaire (PEQ), Hood’s Mysticism Scale (MS), Death Transcendence (DTS)\*, NEO-Five Factor Inventory (NEO-FFI), State-Trait Anxiety (STAI)

\*DTS: 25-items, based on the premise that "death is transcended through identification with phenomena more enduring than oneself."

# Results & Conclusions

Schmid & Liechti (2017)

Increased (@ 1 & 12 months): PEG measures of positive attitudes about life/self, positive mood changes, altruistic/positive social effects, positive behavioral changes, life satisfaction

No relevant changes in personality measures

*Extremely significant and meaningful experience for subjects*



**Conclusions** In healthy research subjects, the administration of a single dose of LSD (200  $\mu\text{g}$ ) in a safe setting was considered a personally meaningful experience that had long-lasting subjective positive effects.