What is a Hallucinogen?

Abraham et al, (1996): “any agent that causes alterations in perception, cognition, and mood as its primary psychobiological action in the presence of an otherwise clear sensorium”

A drug or other substance that produces hallucinations

Also called:

*Psychotomimetics* (mimicking psychosis)

*Psychedelics* (mind-expanding)

*Illusinogens* (generating illusions)

*Schizotoxins* (poison inducing schizoid symptoms)

*Entheogens* (engendering contact with the “god within”)
Some Hallucinogenic History

- Use of natural hallucinogens predates historical record
- Work on psychopharmacology of hallucinogens begins in earnest (1920)
- Albert Hoffman accidentally discovers the effects of LSD (1938-1943)
- Aldous Huxley publishes *The Doors of Perception* (1954)
- Therapeutic research (1960s - 1970s)
- Research increased in 1990s (more outside of U.S.)
LSD (lysergic acid diethylamide)

- From lysergic acid found in ergot, a fungus that grows on rye and other grains.
- One of the most potent mood-altering chemicals.
  - Odorless, colorless, and tasteless
  - Sold on the streets in tablets, capsules, and occasionally in liquid form.
- Usually taken orally but can be injected
- Often added to absorbent paper and divided into small decorated squares with each square representing one dose
- Schedule 1 in 1970
History: LSD & the CIA

- 1953: Project MK-ULTRA
- Truth serum or humiliation drug?
- CIA’s Clandestine Services Department – let’s all try LSD!
History: Law

- Timothy Leary (Galileo of consciousness)
  - Turn on, tune in, drop out

- Like marijuana, LSD became a symbol of 60s counterrevolution
Category 1: Serotonin-like

- Structurally resemble 5-HT
- Examples include
  - LSD (lysergic acid diethylamide)
  - Psilocybin (from “mushrooms”)
  - DMT (dimethyltryptamine - ayahuasca)
Pharmacokinetics (LSD)

Absorption
- Orally (humans)
- Injected (lab animals)
- Easily passes through BBB and is rapidly absorbed into most tissue in the body
- 20-60 min to take effect
- Lasts 4-12 hrs (depending on dose)

Blotter Papers
Pharmacokinetics

Half-Lives vary among different species

- Mice/rats: ~10 minutes
- Cats: ~100 minutes
- Monkeys: ~130 minutes
- Humans: ~109 minutes

Elimination

- ~80% LSD leaves the body primarily through feces 2-3 days after taken
Pharmacodynamics

- LSD primarily functions as a 5-HT agonist
- Evidence suggests that its hallucinogenic effects result from interaction with 5-HT 2A receptors.
- Affects sensory, perceptual, and affective processes.
González-Maesó et al.⁴ find that the metabotropic glutamate receptor 2 (mGluR2) and serotonin 5-HT₂A receptor (2AR) physiologically bind each other, leading to reciprocal regulation of their functions.
Category 2: Catecholamine-like

- Also resemble 5-HT, but act on NE, DA, with amphetamine-type effects
- Examples include:
  - Mescaline (from peyote cactus)
  - DOM (dimethoxy-methamphetamine)
  - Myristin, elemicin (in nutmeg and mace)
Administration

- Absorption: Orally, smoked, IV
- Peyote
  - 5-10 buttons = 200mg
  - 30 buttons = +500mg
- Mescaline sulfate (sulfuric acid)
- Mescaline hydrochloride (hydrochloric acid)
- Mescaline acetate (acetic acid or vinegar)
Category 3: Anticholinergic

- Block muscarinic (metabotropic) receptors
- Atropine works peripherally, causes paralysis
- Scopolamine works in CNS, responsible for hallucinations, delirium, amnesia

- Examples:
  - Belladonna
  - Jimsonweed
**Category 4: Dissociative Anesthetics**

- **Examples:**
  - PCP (blocks GLU/NMDA)
  - Ketamine (an alternative to PCP)
  - Schedule 3
  - Both are non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists.
    - Binding to PCP site on NMDA receptors blocks calcium channels
  - Stimulate the release of DA
  - Ketamine interacts with the opioid receptor.
Hallucinogens

- Some hallucinogens are found in naturally occurring substances
  - cactus
  - morning glory seeds
  - jimson weed
  - nutmeg
  - mushrooms
  - *cannabis used to be classified as a hallucinogen
General Effects

• Early
  – Dizziness, chills, nausea, weakness, twitches, anxiety

• Middle
  – Sympathetic arousal (esp. catecholamine-like)
    • Increased blood pressure, dilated pupils, rapid heart rate
  – Incoordination (muscle weakness)
  – Trembling
  – Blurred vision
  – Increased contrasts
  – Visual patterns
  – Feelings of unreality
General Effects (cont)

• Peak
  – Increased sensory effects
  – Wavelike motions
  – Mood swings
  – Spatial and temporal distortion
  – Loosening of ego boundaries
    • No self/other distinction
  – Synesthesia
  – Euphoria or horror
Good vs. Bad Trips

• Function of set and setting
  – Set: personality, current mental state, expectations
  – Setting: environment

• Bad trip elements
  – Panic
  – Confusion
  – Paranoia
  – Anxiety
  – Helplessness
  – Loss of control
  – Psychosis
General Effects

• Effects depend on (set and setting)
  – the amount taken
  – the user’s past drug experience
  – the manner in which the drug is taken
  – the circumstances under which the drug is taken

• Effects are individualized
  – Range from ecstasy to terror
  – Hallucinations tend to occur at high doses
Hallucinogenesis and DRN Suppression

• Dorsal Raphe Nuclei (DRN) may serve as filtering station—screening out unimportant, irrelevant, or common sensations and perceptions

• LSD is a direct agonist at 5-HT$_1$ autoreceptors in DRN, suppressing activity and may disrupt filter (e.g. LSD can make familiar seem novel (*dehabitation*))

• Hallucinations may be related to dreaming, since inactivity of DRN during sleep triggers REM (dreaming)


**Postsynaptic 5-HT_{2a} Action Instead?**

- DRN activity does not correlate well with behavioral effects of LSD
- A group of 5-HT\textsubscript{1} agonists (e.g. buspirone) are anxiolytics, not hallucinogens
- 5-HT-like and catecholamine-like hallucinogen potency correlates with 5-HT_{2a} affinity
- Downregulation/desensitization/blockade of 5-HT_{2a} receptors blunts LSD effects
- post-synaptic 5-HT_{2A} overdensity is involved in the pathogenesis of depression
17.21 LSD EFFECTS ON DORSAL RAPHE NEURONS. (a) The baseline rate of discharge of a raphe cell during a slow intravenou s infusion of LSD (20 μg/kg) which began where indicated by the arrow. An almost total inhibition of the firing for about two minutes was followed by a gradual recovery. Each deflection is the integrated firing rate during a 10-second sampling period. (b) The effect of iontophoretic administration of 5-HT and LSD. The numbers above the bars are the ejection currents in nA. Recovery was more rapid after 5-HT than after LSD treatment. (c) The effect of iontophoretically applied 5-HT and LSD on a cell in the ventrolateral geniculate nucleus. An intravenous dose of LSD (10 μg/kg) accelerated the firing in this cell. The inhibition by iontophoretic 5-HT during the intravenous infusion was not blocked. Each inflection in this trace was the integrated firing rate during a 1-second sample time. (After Aghajanian and Haigler, 1974.)
Hallucinogenesis and $5$-$HT_{2a}$

- $5$-$HT_{2a}$ receptors found postsynaptically at raphe nuclei targets in limbic areas, visual areas, cortex, and locus coeruleus
- LSD seems to be a $5$-$HT_{2a}$ partial agonist, but effects (excitatory/inhibitory) also depend on target area
- May enhance sensory response of locus coeruleus, contributing to perceptual intensification
- May cause excess unsynchronized Glu activity in cortex, contributing to cognitive and perceptual distortion
Chronic Effects of LSD

- LSD exhibits rapid tolerance, cross-tolerance with mescaline and psilocybin; tolerance lost within several days
- No physical dependence, little psychological dependence
- Laboratory animals do not self-administer LSD
- No withdrawal effects, little evidence of toxicity
- Deaths usually from heart arrhythmias
- Long-term adverse psychological effects probably a result of latent problems revealed/exacerbated by experience
Toxicity & Tolerance

Peyote (mescaline)

- LD50 (humans) unknown
- LD50 varies across species
- Tolerance debated upon
  - Develops for some effects but not others
- Cross-tolerance with LSD, psilocybin
Hallucinogenic Psychotherapy

• Used in shamanic cultures for thousands of years for relief of neurotic and somatic symptoms

• Elucidate underlying problem by projecting unconscious material into consciousness (e.g. symbolically) – psychic loosening

• Forge closer bond between patient and healer

• Facilitate insights by patient, guided and interpreted by healer
Two types of HP emerged in the 1960s

- Psychedelic therapy
  - Emphasized mystical/conversion/bottoming out/consciousness expansion experience
  - One session with heavy dose of LSD (200+ micrograms)

- Psycholytic therapy (mainly European approach)
  - Focuses on enhancing insight to improve psychotherapy
  - Multiple sessions with low doses of LSD (150 micrograms or less)

(LSD threshold for activity ~ 50 mcg)
Psychedelic Results

• Savage et al (1973) tested psychedelic approach
• 96 hospitalized patients with severe, chronic neuroses
• 3 groups: conventional psychotherapy, 50 mcg LSD, 350 mcg LSD
• Single dose after 3-5 weeks preparation
• Tested on psych measures after 6-8 weeks, 6, 12, and 18 months
• Dose-dependent improvements at first evaluation but disappear within 6-18 months
• Males did better with higher doses, females with lower doses
Psycholytic Results

• More clear, consistent results
• Mascher (1967) reviewed studies between 1953-1965
• 68% cases were severe and chronic depressives
• Mean duration of treatment: 4.5 months
• Mean number of psycholytic sessions: 14.5
• 62% of cases were “much” or “very much” improved 2 years later
• 35% slightly worse