HALLUCINOGENS

- Psychedelics (“mind-manifesting”) / entheogens
- class of chemicals that produce a **profound sense of altered reality**
- have been used religiously and worshipped as gods for thousands of years

THE PSYCHEDELICS

- Wide range of effects:
  - Generally, physiologically very benign but psychologically very potent
  - sensorimotor (“pseudo”) hallucinations
    - sensory distortions / illusions
    - synesthesia
    - closed-eye visuals and audio
  - depersonalization
    - ego-loss / out-of-body experiences
- **wide variety of substances / mechanisms**

Major Classes of Psychedelics

- **Classic psychedelics - 5-HT agonists**
  - serotoninergics / indoles / tryptamine
    - LSD, psilocybin (magic mushrooms), DMT / ayahuasca, bufotenine
      - 1P-LSD, AL-LAD, 4-ACO-DMT, 4-HO-MET
- **Psychedelic amphetamines**
  - mixed 5-HT / NE / DA agonists (catecholaminergics / phenethylamines)
    - mescaline, MDMA, DOM, 2CB, etc
- **Dissociatives: glu NMDA receptor antagonists**
  - PCP, ketamine
- **Opiate psychedelic: kappa agonists**
  - salvinorin a
- **Deliriants - ACh antagonists (anti-cholinergics)**
  - atropine, scopalamine (jimsonweed, mandrake, belladonna)

Therapeutic Uses

- In science, 1st used to “model” psychoses - common for therapists to take mescaline, LSD etc
- then to patients - “Psychotherapeutic catalyst” - intense introspection
  - 2 schools of psychedelic therapy in 1950s-60s
    - low dose as an adjunct to therapy (Europe)
    - high does to blow mind (America - over 40,000 patients)

- Psychedelics have far fewer side effects than current psychotropic drugs
  - generally speaking, 1-3 treatments is enough

- meet with treatment team before and after session to go over goals
- set & setting is VERY important

Therapeutic Uses

Overwhelming fear of death in terminal cancer patients

- Psilocybin
  - patient brings pictures of loved ones etc, given headphones and access to “trip-sitters”, process with team afterwards and followups
    - sense of connectedness / one with the universe
    - much more to the world than everyday experiences - seeing “reality”
    - feeling is almost impossible to forget, seems to be retained long-term
    - come to terms with their own death
  - also LSD for anxiety

Depression:

- psilocybin
- ketamine (www.ketamineclinics.com)
  - already FDA approved so doctors can use “off-label”
  - session for depression - 125 mg + 75 mg booster (6-8 hrs)
    - *Once a month for 3 months - 75% remission ???*

Therapeutic Uses

PTSD:

- under effects of MDMA, traumatic story is retold
- brain is full of oxytocin
- story becomes one of love and empathy - moves “narrative” of trauma into a new direction
- MDMA also used similarly in marriage counseling (in 1980s)

Addiction:

- LSD (Bill Wilson), ibogaine, ayahuasca
  - illuminates the “error of your ways”

OCD, and in “normal” people

Johns Hopkins study on <u>healthy</u> subjects

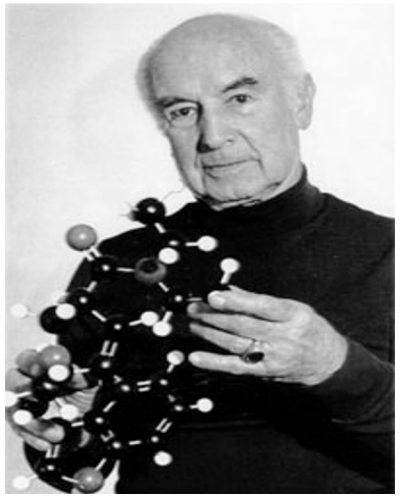
microdosing - cluster headaches, depression, focus, creativity, Alzheimer’s, etc

THE SEROTONINERGIC PSYCHEDELICS

- LSD 1st synthesized in 1938 by the *pharmacognosist* Albert Hofmann at Sandoz Pharmaceuticals from a rye fungus (ergot) as a vasoconstrictor
    - sent off to Pharmacology Dept - they said “no potential, move on”
    - 5 years later, a “thought” came to Hoffman to “re-look” at LSD-25
        - irregular to question Pharmacology Dept, ergot was very expensive, so this project was “odd” to say the least
            - Hoffman said the “LSD chose him”
- April 16, 1943 - re-synthesized
    - (assumed) accidental ingestion of a minute quantity
    - 1st LSD trip (*kykeon* in Eleusinian mysteries of ancient Greece?)

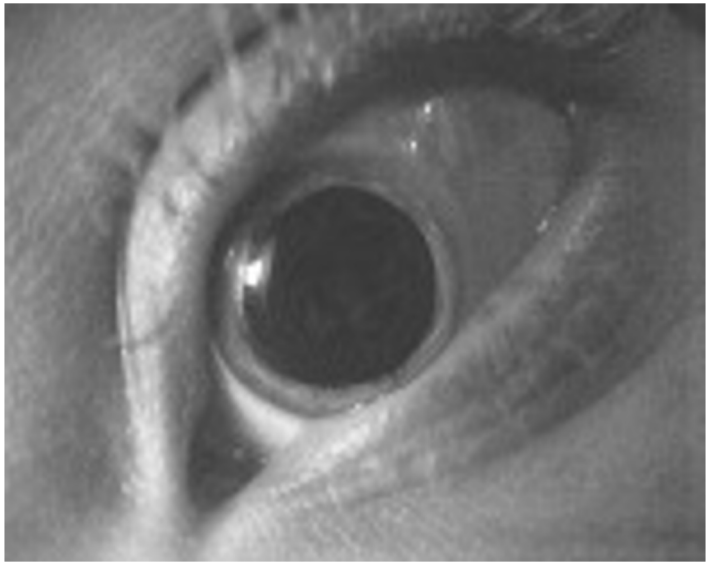
LSD

- April 19, 1943, 4:20 pm - ingested .25 mg (250 micrograms) on purpose
    - 1st intentional trip (“Bicycle Day”)
- used by psychiatrists, artists, hippies and the government ever since
- marketed by Sandoz to psychiatrists - very popular (over 40,000 patients)



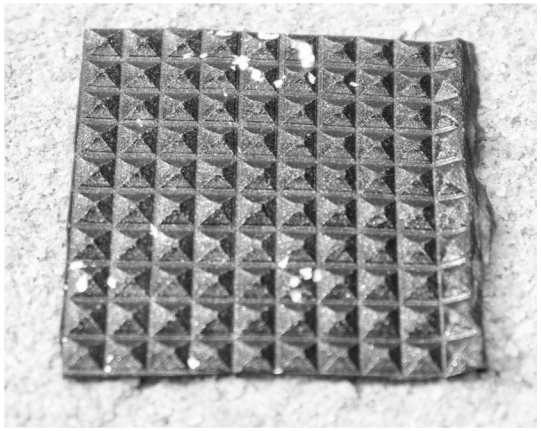
LSD

- **Effects**
  - 3 dose-dependent phases to a classic psychedelic "trip"
    - *"somatic" phase:* CNS / PNS stimulation, increased body temp, dilated pupils, agitation
    - *"sensory" phase:* sensory distortions / pseudohallucinations
    - *"psychic" phase*: loss of ego (too much > "bad trip")



LSD

- **Pharmacokinetics**:
  - usually taken orally



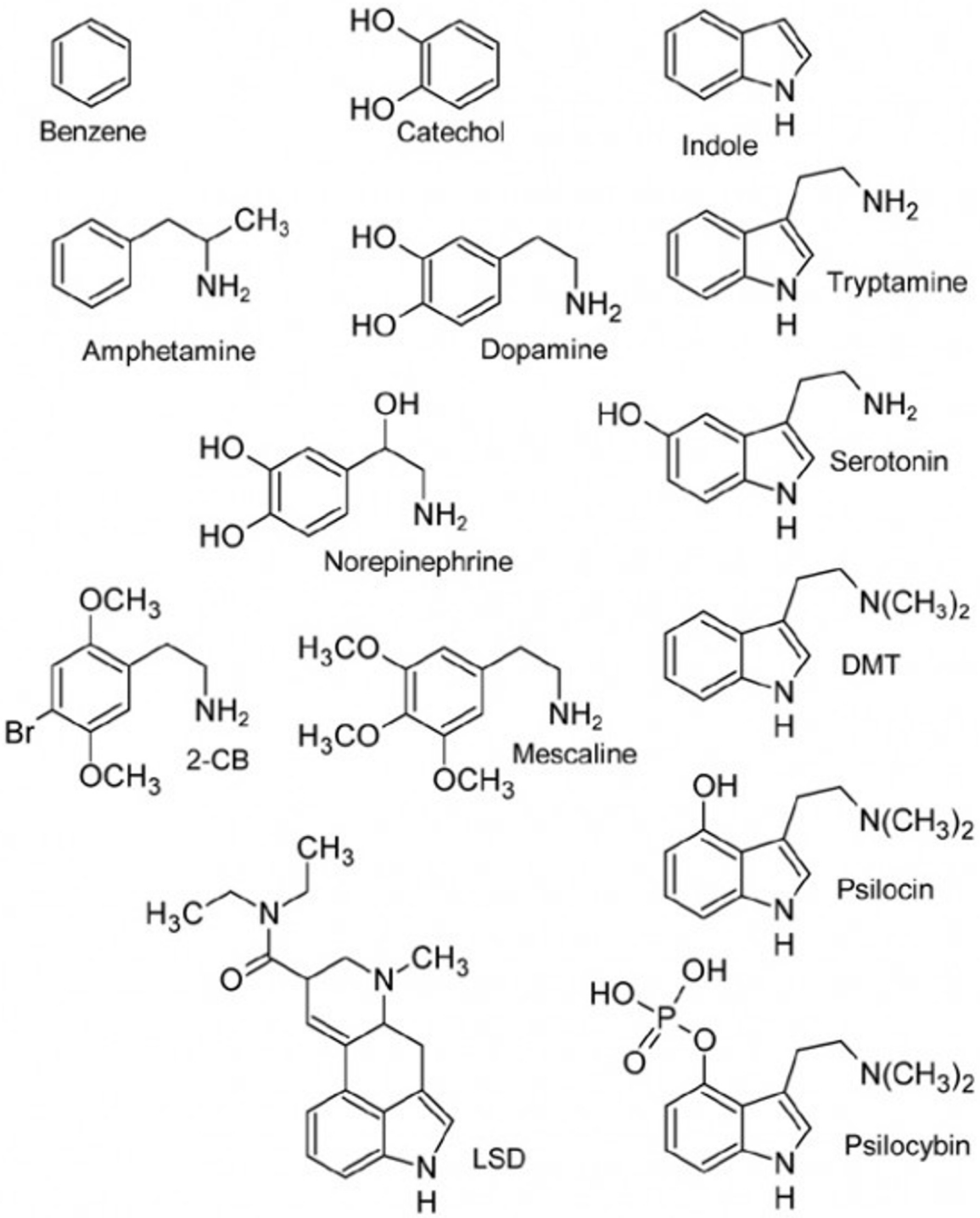
- effective dose ~50 MICROgrams (.05 mg) / lethal dose ~14 mg??? (at least 280 doses???)
  - therapeutic ratio of at least 280 to 1 (*pharmacologically* very safe)
- average dose today ~50-100 micrograms
  - when legal (until 1966), an average dose was ~250 micrograms (.25 mg)
  - records of accidental ingestion of 7 mg (~70 doses) and 40 mg (~400 doses)
    - 7 mg people were studied for 12 years, no adverse effects

LSD

- **Pharmacokinetics**:
  - first effects felt in ~60 min
    - peak plasma levels in ~3 hrs
      - effects last 6-8 hrs
  - metabolites difficult to detect in urine because of low levels

LSD

- Pharmacodynamics:
  - partial agonist of 5-HT_{2A} & 5-HT_{2C} receptors
  - all are structurally similar to 5-HT
    - act as partial <u>agonists</u> to the 5-HT_{2A} receptors
      - a “lid” covers the receptor and holds the LSD there for hours
  - especially active in the pontine (dorsal) raphe nucleus
    - “filters” irrelevant incoming sensory stimuli
    - may allow a flood of stimuli (synesthesia, etc)


Benzene
HO
HO
Catechol
N
H
Indole
CH3
NH2
Amphetamine
HO
HO
NH2
Dopamine
NH2
N
H
Tryptamine
OH
HO
HO
NH2
Norepinephrine
HO
NH2
N
H
Serotonin
OCH3
Br
NH2
OCH3
2-CB
H3CO
H3CO
NH2
OCH3
Mescaline
N(CH3)2
N
H
DMT
CH3
H3C
N
O
N
CH3
N
H
LSD
OH
N(CH3)2
N
H
Psilocin
HO
OH
P
O
O
N(CH3)2
N
H
Psilocybin

LSD

- **Tolerance:**
  - tolerance (and cross-tolerance for other psychedelics) rapidly develops
  - effectiveness returns after a few days
    - self-limiting behavior
  - no physical dependence / withdrawal effects
- **Too Much:**
  - inducement of psychotic states in predisposed individuals
  - depression
  - “drop out” of society
  - Hallucinogen persisting perception disorder (HPPD)
    - very rare - primarily chronic visual disturbances
    - may be brought on by the dis-inhibition of the COMT enzyme in the breakdown of catecholamines, resulting in sensory gating disruption
  - “flashbacks” - very rare, usually isolated and induced by set / setting

THE "NATURAL" 5-HT PSYCHEDELICS

- **DMT (dimethyltryptamine)**
  - short acting, naturally occurring psychedelic
  - found in human brain (metabolite of 5-HT)
    - partial agonist of 5-HT_{2A} & 5-HT_{2C} receptors
  - pure DMT typically snorted or smoked (not active orally)
    - DMT is metabolized in the gut by Mono-Amine Oxidase
  - very intense, but short, LSD-like experience (over in ~30 minutes)
  - found in many South American plants

- **ayahuasca** - drink used orally in Amazon religious ceremonies consisting of a blend of plants containing DMT and harmine

- **harmine** is a natural MAO inhibitor

- together - allows oral administration, potentiates & prolongs effect

5-HT PSYCHEDELICS IN A NUTSHELL

- 5-HT$_{2A}$ receptors are the most likely site of action
- expressed on the pyramidal neurons of cortical layer 5
  - long axons connecting wide areas of cortex and thalamus

*

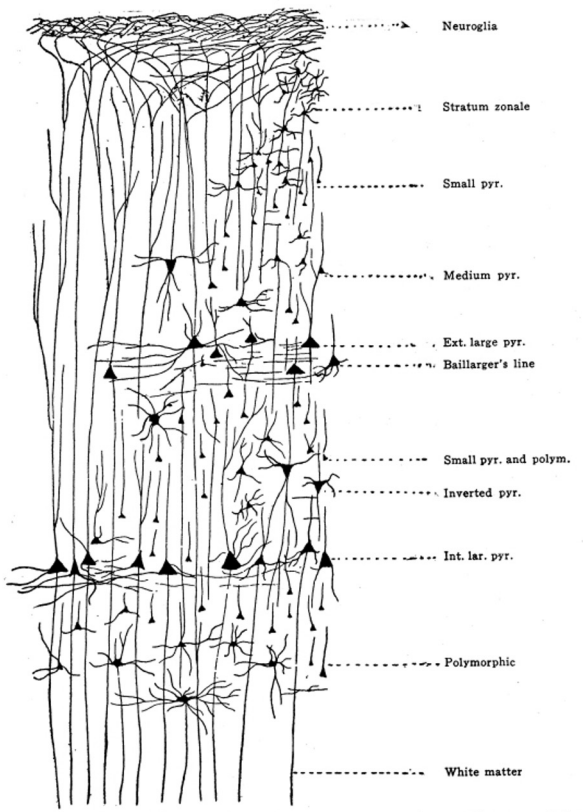
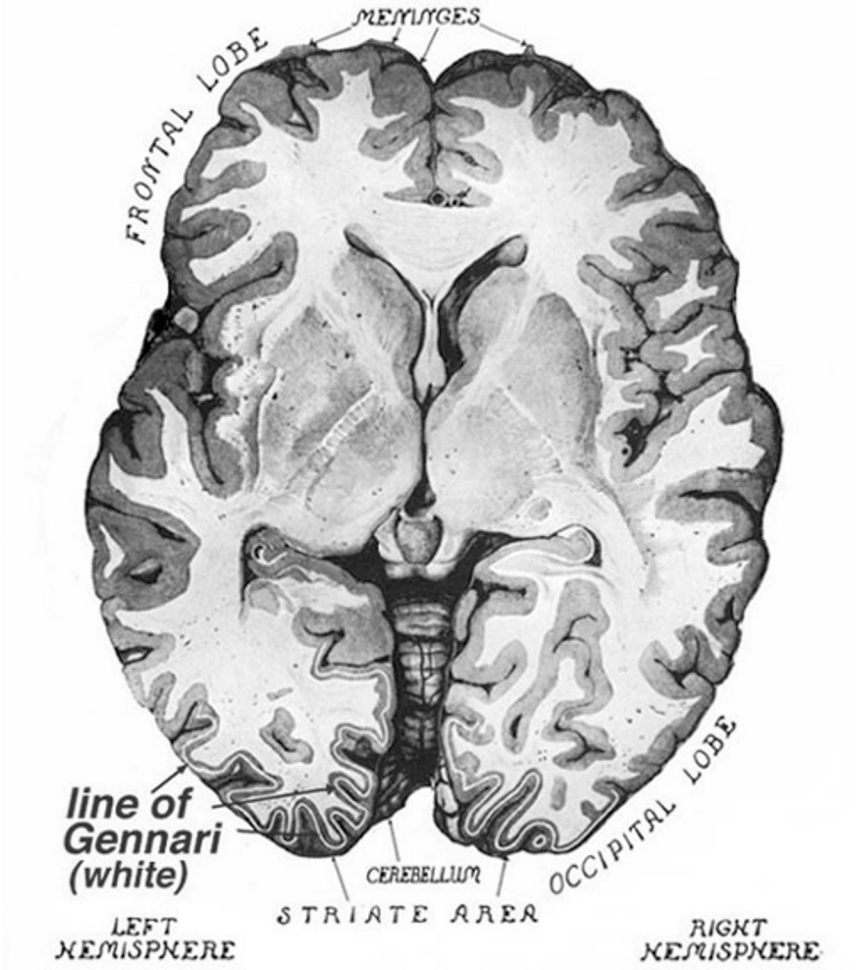


Fig. 5. Diagram of the layers of the typical cerebral cortex. The neuroglia appears at the external surface. The first layer of the cortex contains the spindle and polymorphic cells. (See Fig. 3.) . Among these cells the dendrites of other cells, and the axons and collaterals of the inverted pyramids of Martinotti branch freely. The layer of small pyramids lies next. The dendrites of these reach the first layer; the axons exhaust themselves branching among the deeper layers. The third layer is characterized by the medium pyramids. The relations of these are as the small pyramids. The fourth layer is characterized by the large pyramids. The axons of these may enter the white matter and pass to other parts of the nervous system. The fifth layer includes small pyramids and polymorphic cells. The sixth layer contains large pyramidal cells, and the axons of these may enter the white matter. The seventh layer contains spindle and polymorphic cells, whose axons also may reach the white matter and pass to other parts of the nervous system. Small pyramidal cells, multipolar cells, Golgi Type II cells, and inverted pyramids may be found through all except the first layer. The line of Baillarger coincides with the external layer of large pyramids.



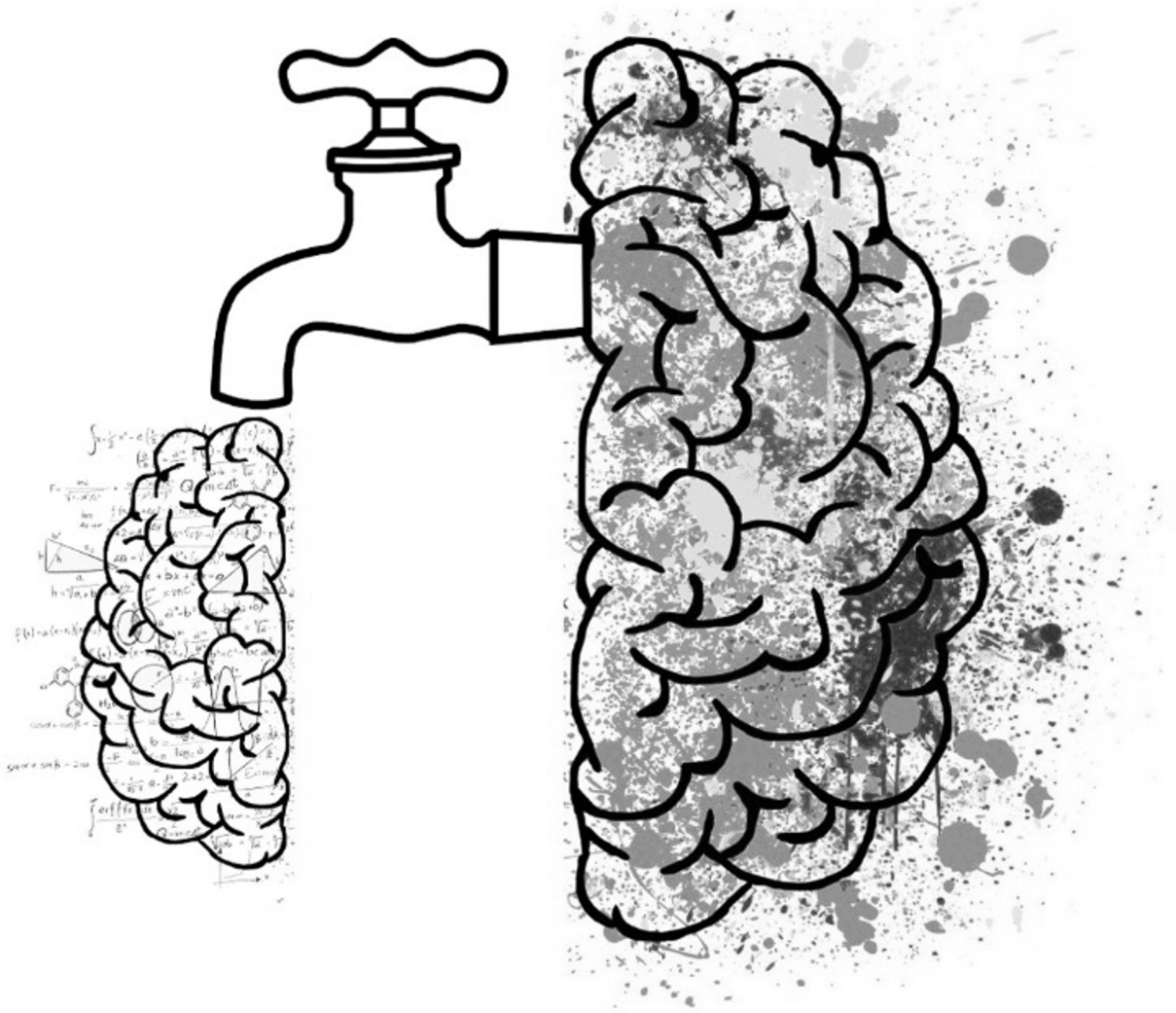


FIGURE 3 | Aldous Huxley's "cerebral reducing valve." On the 'inlet' (right) side of the cerebral reducing valve is a vast ocean of all possible perceptual, emotional, and cognitive experiences. On the 'outlet' (left) side is our moment-to-moment stream of experience in normal waking life. Mechanisms inside the valve 'reduce' the character and contents of experience, 'canalizing' the ocean of possible experience into a more limited stream of waking consciousness aimed at maximum biological utility.

5-HT PSYCHEDELICS IN A NUTSHELL

- the brain is basically a group of cells that oscillate in response to external stimuli

- these long pyramidal neurons induce rhythmic oscillations in brain activity that “bind” sensory perceptions together with synchronizing neural firing

    - "neurons that fire together wire together"

- by acting on 5-HT_{2A} receptors on these neurons, psychedelics may induce abnormal / distorted oscillation patterns in the brain

    - senses become “unbound” and loss of ego occurs (?)

*

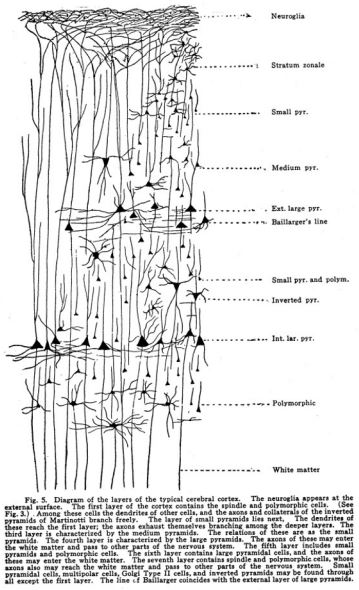
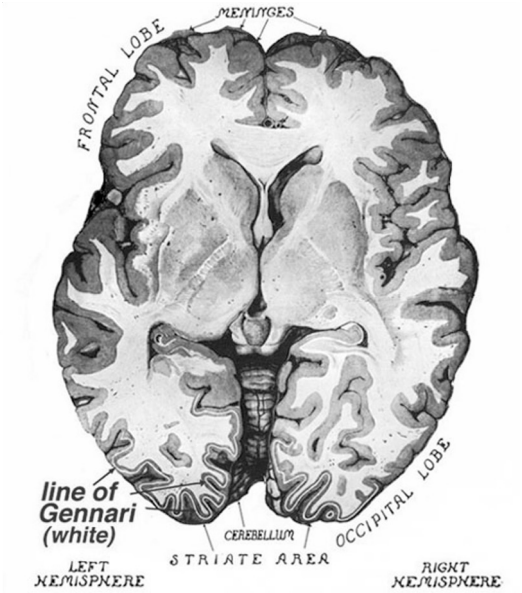
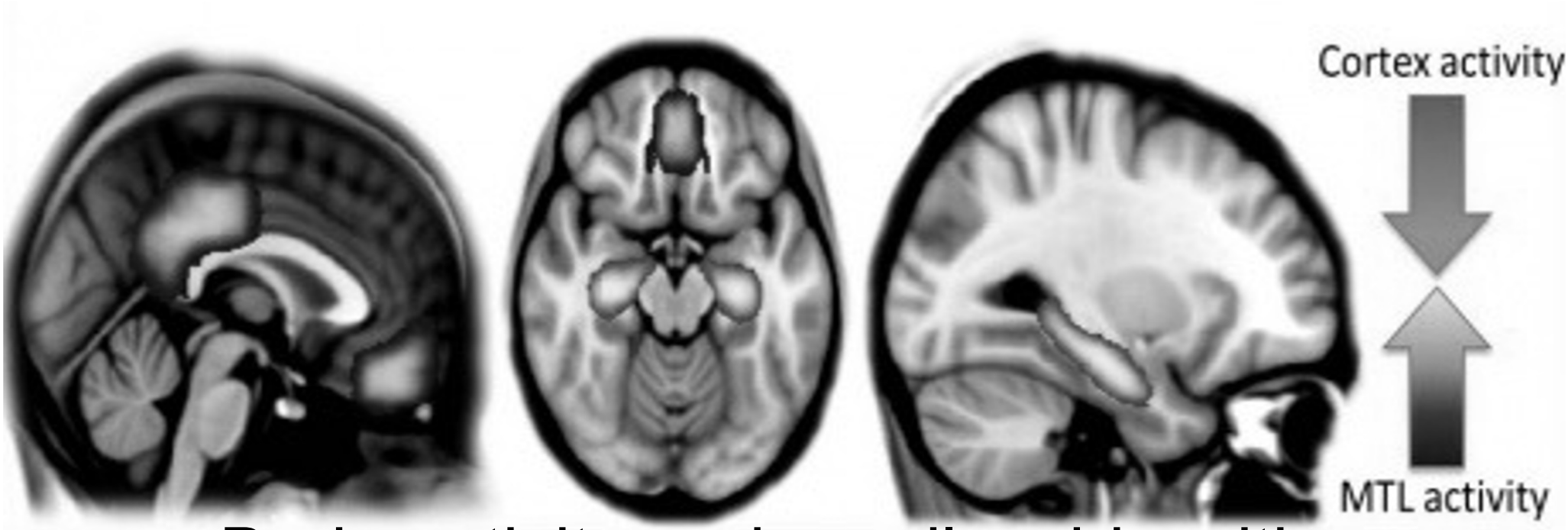


Fig. 5. Diagram of the layers of the typical cerebral cortex. The neuroglia appears at the external surface. The first layer of the cortex contains the spindle and polymorphic cells. (See Fig. 3.) Among these cells the dendrites of other cells, and the axons and collaterals of the inverted pyramids of Martinotti branch freely. The layer of small pyramids lies next. The dendrites of these reach the first layer; the axons exhaust themselves branching among the deeper layers. The third layer is characterized by the medium pyramids. The relations of these are as the small pyramids. The fourth layer is characterized by the large pyramids. The axons of these enter the white matter and pass to other parts of the nervous system. The fifth layer includes small pyramids and polymorphic cells. The sixth layer contains fusiform pyramidal cells, and the axons of these may enter the white matter. The seventh layer contains spindle and polymorphic cells, whose axons also may reach the white matter, and pass to other parts of the nervous system. Small pyramidal cells, multipolar cells, Golgi Type II cells, and inverted pyramids may be found through all except the first layer. The line of Baillarger coincides with the external layer of large pyramids.



5-HT PSYCHEDELICS IN A NUTSHELL

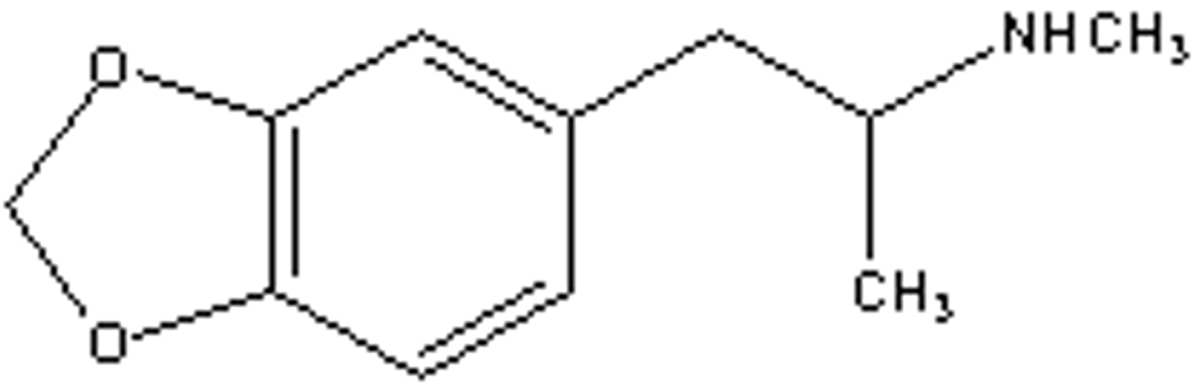


Brain activity under psilocybin with a decrease (blue) in “executive” brain regions (*PFC/ **parietal cortex) and an increase (orange) in memory and emotion regions (***medial temporal lobe*)

*ego / **attention / ***religiosity

THE CATECHOLAMINERGIC PSYCHEDELICS

- structurally similar to:
  - the catecholaminergic NTs (DA / NE)
  - amphetamines
    - adding a "methoxylated" molecular group (O–CH3) to the amphetamine molecule creates a “psychedelic stimulant”



MDMA; 3,5-Methylenedioxymethamphetamine

THE CATECHOLAMINERGIC PSYCHEDELICS

- also, possible 5-HT_2 receptor agonists
  - "mixed" DA / 5-HT agonists
    - DA activity mediates psychostimulant effects
      - energy, arousal, sociability, etc.
    - 5-HT activity probably responsible for psychedelic properties

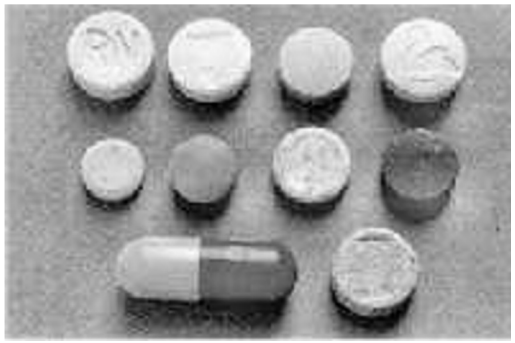
THE CATECHOLAMINERGIC PSYCHEDELICS

- **Mescaline**

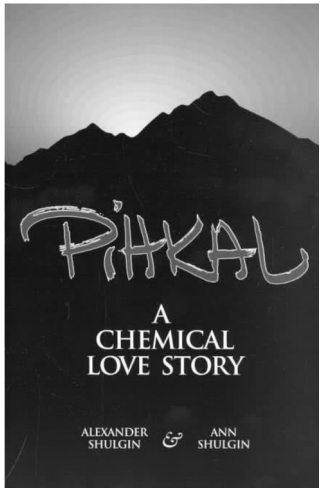
- constituent of peyote and san pedro cactus in the Southwest
- used traditionally by Aztecs and Native Americans
- still legal for members of the Native American Church
- used as a sacrament in religious ceremonies
- 1st psychedelic compound to be synthesized in early 20th century

THE CATECHOLAMINERGIC PSYCHEDELICS

- **Synthetic mescaline / amphetamine derivatives:**
  - methoxylated amphetamine derivatives / “psychedelic stimulants” / “designer drugs”:
    - MDMA (Ecstacy), DOM (STP), MDA, DMA, MDE, TMA, AMT, 5-MeO-DIPT, 25I-NBOMe (2C-I-NBOMe - N bomb)
      - popular “club drugs” - sociability and euphoric feelings (”love drugs”)
        - at low doses, primarily stimulants
        - at higher doses, primarily psychedelics



- **Too Much**
  - in 80s, use of MDMA was “self-limiting” - relatively safe
  - now taken in large doses with other drugs in crowded environments
    - stimulant action causes hyperthermia / cardiac arrhythmia
    - decreases in 5-HT / DA (toxic?)
    - depression



THE CATECHOLAMINERGIC PSYCHEDELICS

- **Nutmeg / Mace Derivatives**
  - *myristin*, *elemicin* - structurally similar to mescaline
  - 1-2 teaspoons of spice - effects felt for several hours
  - unpleasant side effects - most don’t take twice

THE NMDA ANTAGONIST PSYCHEDELICS

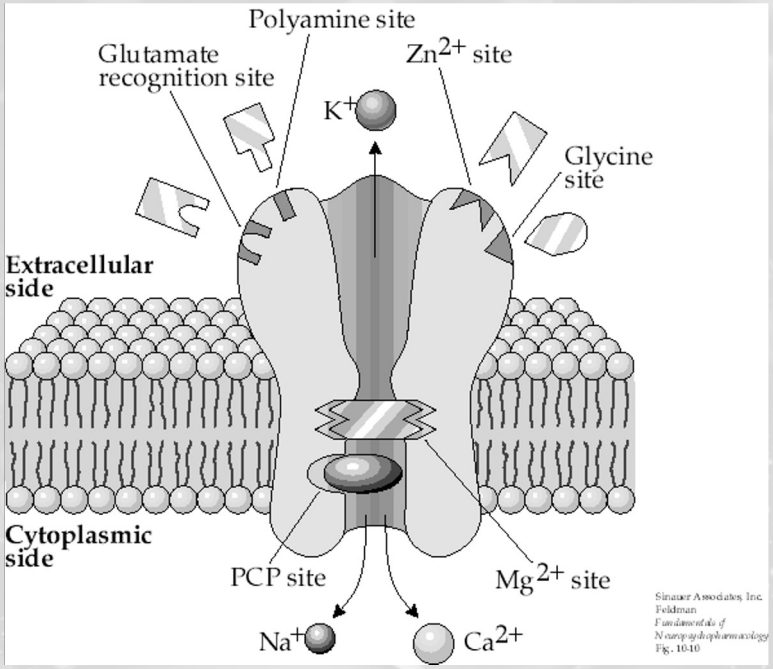
- Glutamate receptor (NMDA) Antagonists:
  - "psychedelic anesthetics":
    - *Phencyclidine* (PCP, angel dust)
    - *ketamine* (special K)
    - *Dextromethorphan* (Robtussin)
    - nitrous oxide
- unique pharmacology - not related to the other psychedelics
  - do not *directly* involve 5-HT, ACh, or DA

THE NMDA ANTAGONIST PSYCHEDELICS

- Both PCP and ketamine (and nitrous oxide) used as anesthetics
- analgesic
- produce intense psychedelic state during awakening
    - re-emergence phenomenon
        - typically **not** in pre-adolescents
    - "dissociative" state similar to schizophrenia (used as an animal model)
        - schizophrenia is associated with NMDA receptor *hypo*function
- amnesia (lots of NMDA receptors in the hippocampus)
- activates reward centers (e.g., nucleus accumbens)
    - only psychedelics to be self-administered by monkeys
    - ketamine is known as "psychedelic heroin"

THE NMDA ANTAGONIST PSYCHEDELICS

- **Pharmacodynamics**:
  - "non-competitive antagonists" of NMDA glu receptors



- do not bind at glu site
- block ion flow from inside the channel
- another site on the outside - inhibits opening of channel
- also interact with opioid receptors
- "serotoninergic" psychedelics also block NMDA receptors

THE OPIOID PSYCHEDELIC

- **salvia divinorum** - “diviner’s sage” / “magic mint”

- traditionally used by the Mazatec indians
- (currently) legal
- typically smoked - produces an intense, very short psychedelic trip
- or chewed - less efficient, slower, less intense

THE OPIOID PSYCHEDELIC

- **salvinorin a** - chemically distinct from all other psychedelics
  - *kappa* opioid receptor (found in cortex) agonist
  - no effects on 5-HT receptors
  - smoked dose: 200-500 MICROgrams (.2-.5 mg) of active drug
  - almost as potent as LSD
  - most potent naturally-occurring psychedelic
  - anecdotally used as an antidepressant

THE ANTI-CHOLINERGIC PSYCHEDELICS

- used for thousands of years - induce a sensation of flying (witches)
  - atropa belladonna: belladonna / deadly nightshade
  - datura stramonium: jimsonweed
  - mandrake

Therapeutic Uses

Inducing the experience without chemicals:

- meditation
- yoga
- rhythmic / hypnotic music
- isolation / sensory deprivation tanks