Psychedelics in science and medicine
What are psychedelics?

DMT

LSD

Psilocin

Serotonin

Ergot on Rye
How do they work?

Importance of serotonin 2A receptor

1. 

2. 5-HT2A blockade ↑ psychedelic effects ↓

3. 5-HT2A in cortex

4. 5-HT2A on Layer 5 neurons

References:

- Glennon et al. 1984
- Erritzoe et al. 11
- Vollenweider et al. 99; Kometer et al. 12
- Weber & Andrade 10

Additional notes:

- ↑ 5-HT2AR affinity
- Potency →
- LSD

Graphs and images depict the relationship and distribution of 5-HT2A receptors and their effects on the brain.
Why are psychedelics interesting?

1. Effects on consciousness

Enduring changes in outlook & personality

- 67% top five most meaningful experiences of whole of their lives
- 79% wellbeing ↑
- Increased trait openness > 1 year after (Griffiths et al. 2006, 08, MacLean et al. 11)

2. Therapeutic promise

- Depressed depression scores at 6 months (Grob et al. 11)
- 80% abstinence from smoking at 6 months (Johnson et al. 14)
- Decreased drinking at 9 months (Bogenschutz et al. 15)
- Decreased anxiety at 12 months (Gasser et al. 14)
- Less distress & suicidality in US (Hendricks et al. 15)
5-HT2AR-mediated effects in animals

- 5-HT2AR-stim ↓ perseverance (‘repeating’) ↑
  (Clarke et al. 04, 07; Boulougouris et al. 08)

- LSD/2A stim ↑ cognitive flexibility & learning ↑
  (King et al. 1974; Harvey et al. 03; Romano et al. 10)

Normal BDNF (vehicle) 2A stim → BDNF ↑

- 5-HT2AR agonism ↑ neural plasticity ↑
  (Vaidya et al. 97; Gerwitz et al. 02; Fankel et al. 02)
How do psychedelics affect the human brain?

**ASL study with psilocybin**
- 15 healthy volunteers
- Mean age = 34 ± 4
- 18 minutes scan x 2
- Task-free ‘rest’
- 2mg psilocybin IV

**BOLD study**
- 15 healthy volunteers
- Mean age = 32 ± 9
- 12 minutes scan x 2
- Task-free ‘rest’
- 2mg psilocybin IV

**Magnetoencephalography (MEG)**
- 15 healthy male volunteers
- Mean age 35 ± 2

**fMRI work with MDMA**
- 25 healthy volunteers (5 females)
- Double-blind, placebo-controlled. Two scans, 7 days apart
- 100mg MDMA-HCL orally administered 45 mins pre-functional scanning
- 60 mins functional scanning
- Resting state ASL, BOLD resting state
LSD fMRI & MEG study

- 20 healthy psychedelic experienced volunteers
- 16 males, 4 females, mean age 31 + 8.
- Scanned twice: placebo & LSD, two weeks apart.
- 75mcg LSD (I.V.)
- Music

LSD/placebo

60 minutes → 80 minutes → 80 minutes

60 minutes

fMRI

MEG

Psychology tasks
“Everything became very fragmented; things were all in bits and it was very hard to hold it all together in a coherent stream.”

“That was real ego-death stuff, I only existed as a concept, as an idea.”

“The feeling of no boundaries, I did not know where I ended and my surroundings began. Somehow I was able to comprehend what oneness is.” (Griffiths et al.)
Two important features of the brain

1. Integration

2. Segregation

• Both increase through development

(Dosenbach et al. 10; Thomason et al. 08; Stevens et al. 09; Wylie et al. 2014, Yu et al. 14; Uddin et al. 11; Fransson et al. 2007; Fair et al. 2008; Gao et al. 2009; Supek et al. 2010)
What's resting-state functional connectivity?

$r = 0.84$

$r = 0.06$

BOLD signal vs. time (min)
Network disintegration on LSD

Intra-RSN metrics (LSD minus placebo): CBF, integrity, signal variance

1. VisM
2. VisL
3. VisO
4. AUD
5. SM
6. DMN
7. PAR
8. DAN
9. SAL
10. POP
11. IFP
12. rFP
Network desegregation on LSD

b) **Inter-RSN RSFC/segregation**

- **Placebo**
- **LSD**
- **LSD minus placebo**
Network desegregation with **psilocybin** (left) But not MDMA (right)

**Principles:**
1. Desegregation
2. Anti-hierarchical: Low level networks high-level networks Segregation ↓

Roseman et al. 14
Psychedelic’s action: Key principles

1. Network **disintegration**

2. Network **desegregation**
The regressive brain

Integration & segregation

Disintegration & desegregation

Regression

Maturation

Integration & segregation ↑ development ↑

(Dosenbach et al. 10; Thomason et al. 08
Stevens et al. 09; Wylie et al. 2014, Yu et al. 14; Uddin et al. 11; Fransson et al. 2007; Fair et al. 2008; Gao et al. 2009; Supekar et al. 2010)
Infant v psychedelic consciousness

Not in entire forgetfulness,
And not in utter nakedness,
But trailing clouds of glory do we come
From God, who is our home:

Heaven lies about us in our infancy!

Shades of the prison house begin to close
Upon the growing boy”

30mg psilocybin → ‘Complete mystical experience’ in 22 of 36
(Griffiths et al. 06)

Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance

R. R. Griffiths • W. A. Richards • U. McCann • R. Jesse
Ego-dissolution $\rightarrow$ transformative experiences

Religious/spiritual/mystical experience:

- Loss of self  
  (James)
- Sense of oneness  
  (Stace)
DMN disintegration ↑

ego disintegration ↑
PH-PCC disconnection ↑
ego disintegration & altered meaning ↑

PH-PCC FC v subjective effects

Ego-disintegration vs Altered meaning

Decreased PH-PCC FC under LSD v plac
Altered meaning
1. “Objects in my surroundings touched me more emotionally.”
2. “Things in my surroundings had a new or alien meaning.”
3. “Some unimportant things acquired special meaning.”

Reviews and Overviews

Psychosis as a State of Aberrant Salience: A Framework Linking Biology, Phenomenology, and Pharmacology in Schizophrenia

Shitij Kapur, M.D., Ph.D., F.R.C.P.C.

Objective: The clinical hallmark of schizophrenia is psychosis. The objective of this overview is to link the neurobiology (brain), reflect a direct experience of the aberrant salience of internal representations. Antipsychotics “dampen the salience” of these

Schizophrenia: A Disconnection Syndrome?

Karl J. Friston and Christopher D. Frith

We review the evidence of pathophysiological changes in the prefrontal and temporal cortices of schizophrenic subjects and of abnormal integration of the physiological dynamics in these two regions. The argument we develop is that some schizophrenic phenomena are best understood in terms of abnormal interactions between different areas, not only at the levels of physiology and functional anatomy, but at the level of cognitive and sensorimotor functioning. We discuss recent electrical stimulation of motor cortex [e.g., Ferrier, 1875], considered the excitation method inconclusive, in that movements elicited might have originated in related pathways or current could have spread to distant centres [Phillips et al., 1984]. This dialectic, functional segregation vs. functional integration, persists today and forms the basis for this
• 5-HT2AR ↑ in depression (e.g. Bhagwaga et al. 06)

• 5-HT depletion → 5-HT2AR↑ (Cahir et al. 07)

• 5-HT2AR binding ↑ Trait neuroticism ↑ (Frokjaer et al. 2010)

• 5-HT2AR binding ↑ Pessimism in depression ↑ (Meyer et al. 2003)

• 5-HT2AR blockade → psilocybin-induced positive mood ↓ (Kometer et al. 12) & MDMA ↓ (van Wel et al. 12)

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Deficient 5-HT2AR stimulation → Habitual negative thinking?

Psychedelics → 5-HT2AR stim
Psilocybin for depression

- Depression affects 150 M people worldwide
- Estimated to become the leading contributor to the global burden of disease by 2030
  - Most costly brain disorder in Europe (€118B 2004)
    - Leading cause of premature death
  - 20% patients unresponsive to all treatment

“After I have had an experience with LSD, Magic Mushrooms, or Ketamine, there will be several weeks after where I feel as if I'm a brand new person, more so with Mushrooms, followed by LSD, and the least so with Ketamine. Magic Mushrooms have helped me in many other ways as well. It lets me recognize some of the negative patterns in my life and change them, and no SSRI can do that.”

(Carhart-Harris & Nutt, 2010)
Molecular action, societal change?

1. Network **disintegration**

2. Network **desegregation**

3. Collapse of **hierarchy**

- Trait openness ↑ > 1 yr post psilocybin (MacLean et al. 11)
- Traits openness ↑, conscientious ↑, optimism ↑ 2 weeks post LSD (Carhart-Harris et al. in prep)

• Psychedelic experience → altered political perspectives???
“Psychedelics are illegal not because a loving government is concerned that you may jump out of a third story window. Psychedelics are illegal because they dissolve opinion structures and culturally laid down models of behaviour and information processing.”

(Terrance McKenna)
"Why if the trials were worthwhile six months ago, why aren’t they worthwhile now? We keep going around and around... If I could get a flat answer about that I would be happy. Is there a misunderstanding about my question?

I think perhaps we have lost sight of the fact that LSD can be very, very helpful in our society if used properly.”

Robert F Kennedy (1925-1968)

Psychodelics: an alternative to ‘bad pharma’ in psychiatry?
Thank you