



Psychedelics in science and medicine



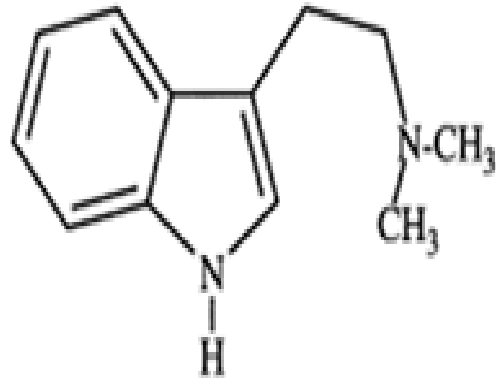
REPUBLIKA SLOVENIJA
MINISTRSTVO ZA IZOBRAŽEVANJE,
ZNANOST IN ŠPORT



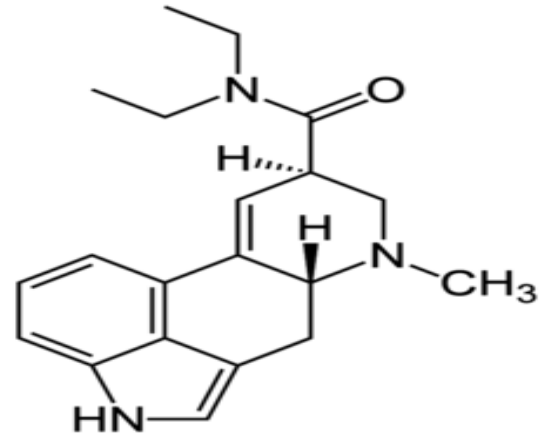
Naložba v vašo prihodnost
OPERACIJO DELNO FINANCIRA EVROPSKA UNIJA
Evropski socialni sklad

Robin Carhart-Harris. Ljubljana. 16th May 2015

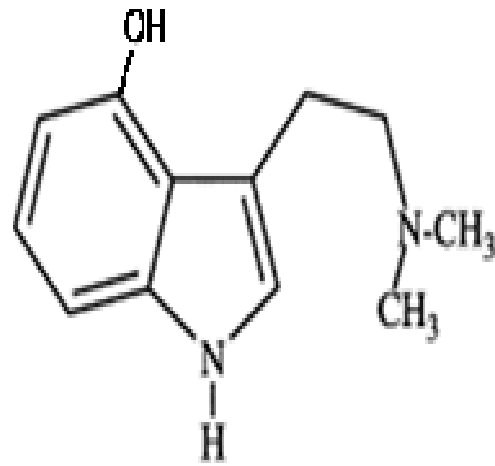
What are psychedelics?



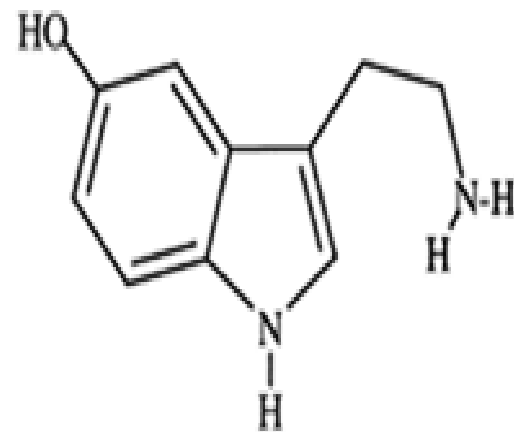
DMT



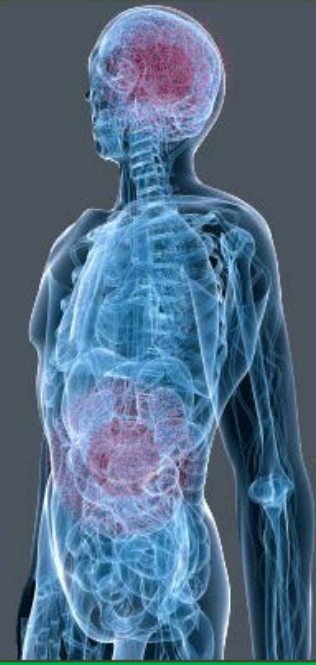
LSD



Psilocin



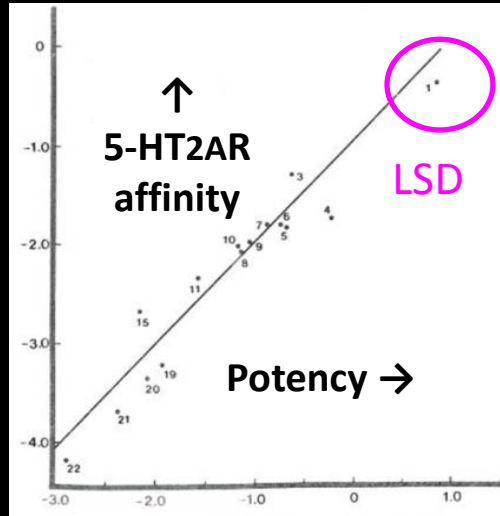
Serotonin



How do they work?

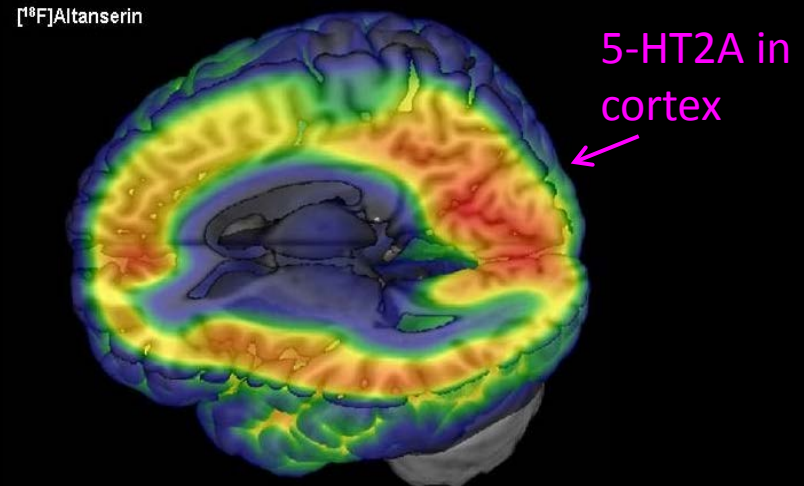
Importance of serotonin 2A receptor

1.



Glennon et al. 1984

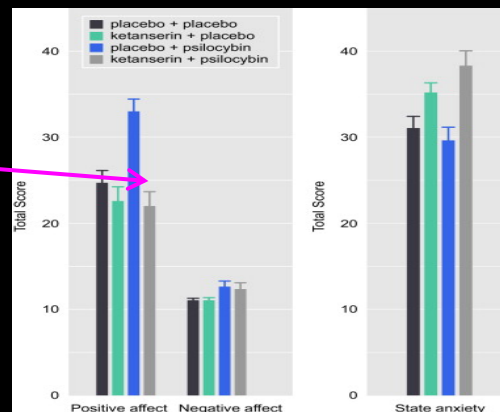
3.



Erritzoe et al. 11

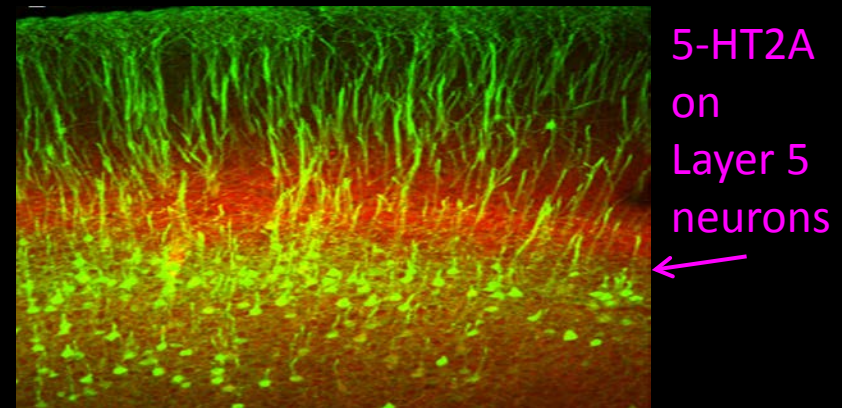
5-HT2A
blockade ↑
psychedelic
effects ↓

2.



Vollenweider et al. 99; Kometer et al. 12

4.



e.g. Weber & Andrade 10

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)

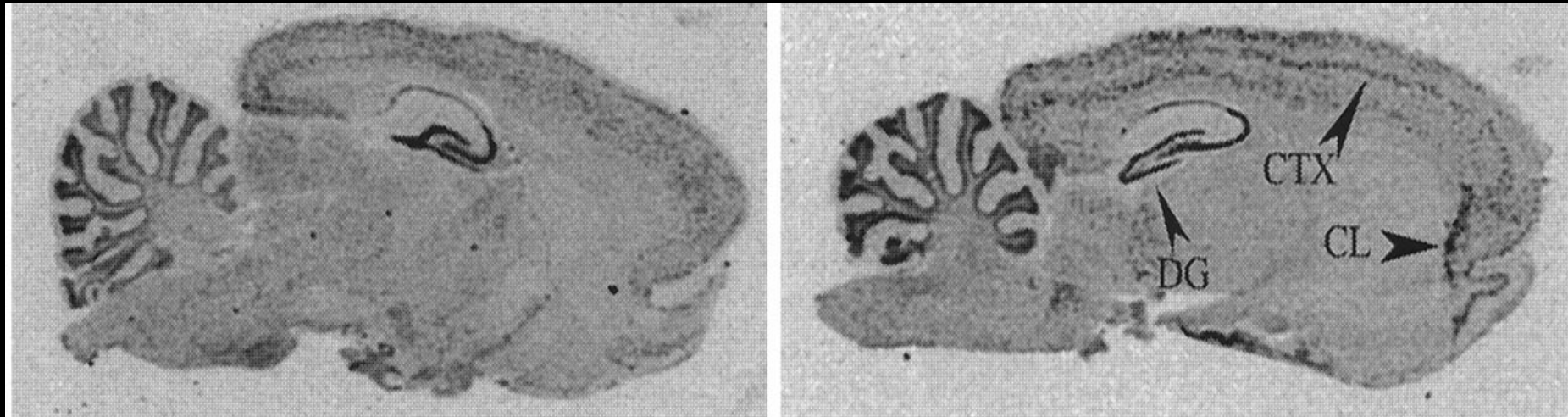


5-HT2AR-mediated effects in animals

- 5-HT2AR-stim ↓ perseveration ('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

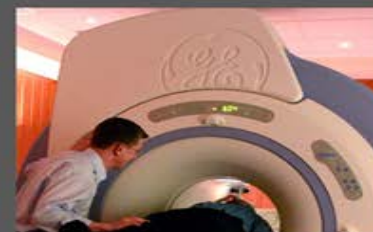


15 healthy volunteers
Mean age = 34 ± 4
18 minutes scan x 2
Task-free 'rest'.
2mg psilocybin IV



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

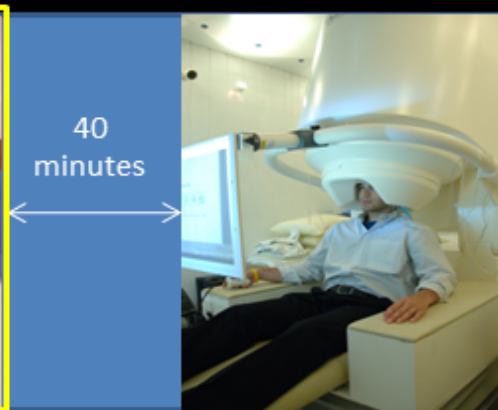


60 minutes



fMRI

80 minutes



MEG

80 minutes



Psychology tasks

Psychological effects

“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



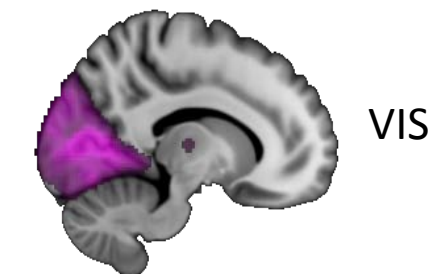
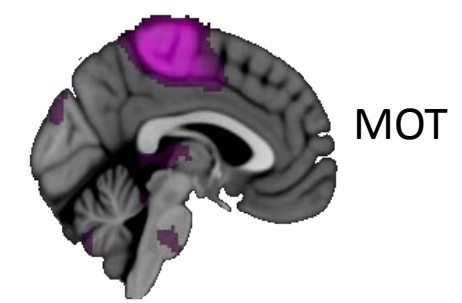
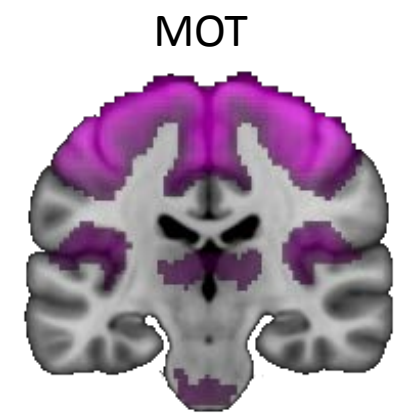
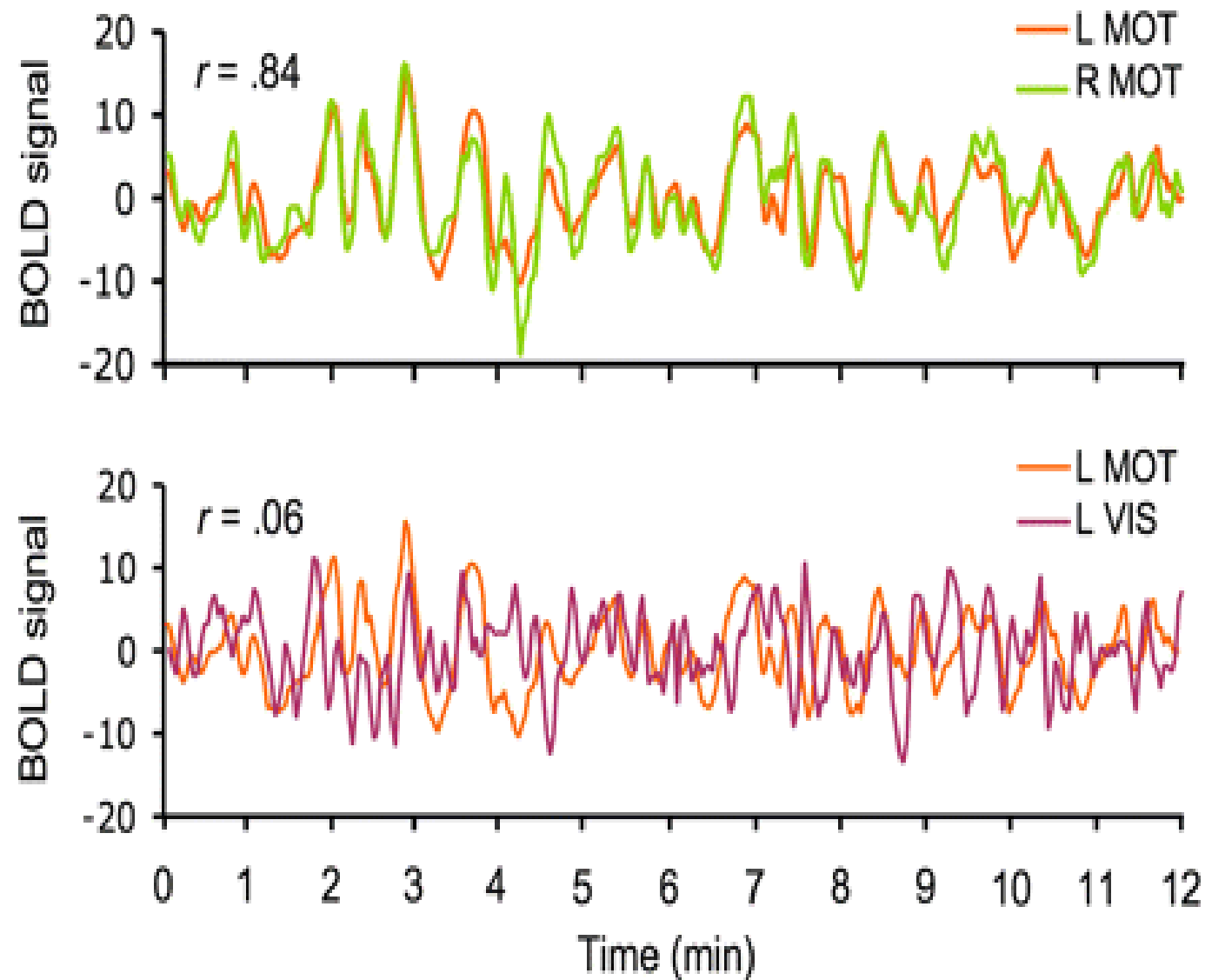
2. Segregation

- 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; Supekar et al. 2010)



What's resting-state functional connectivity?

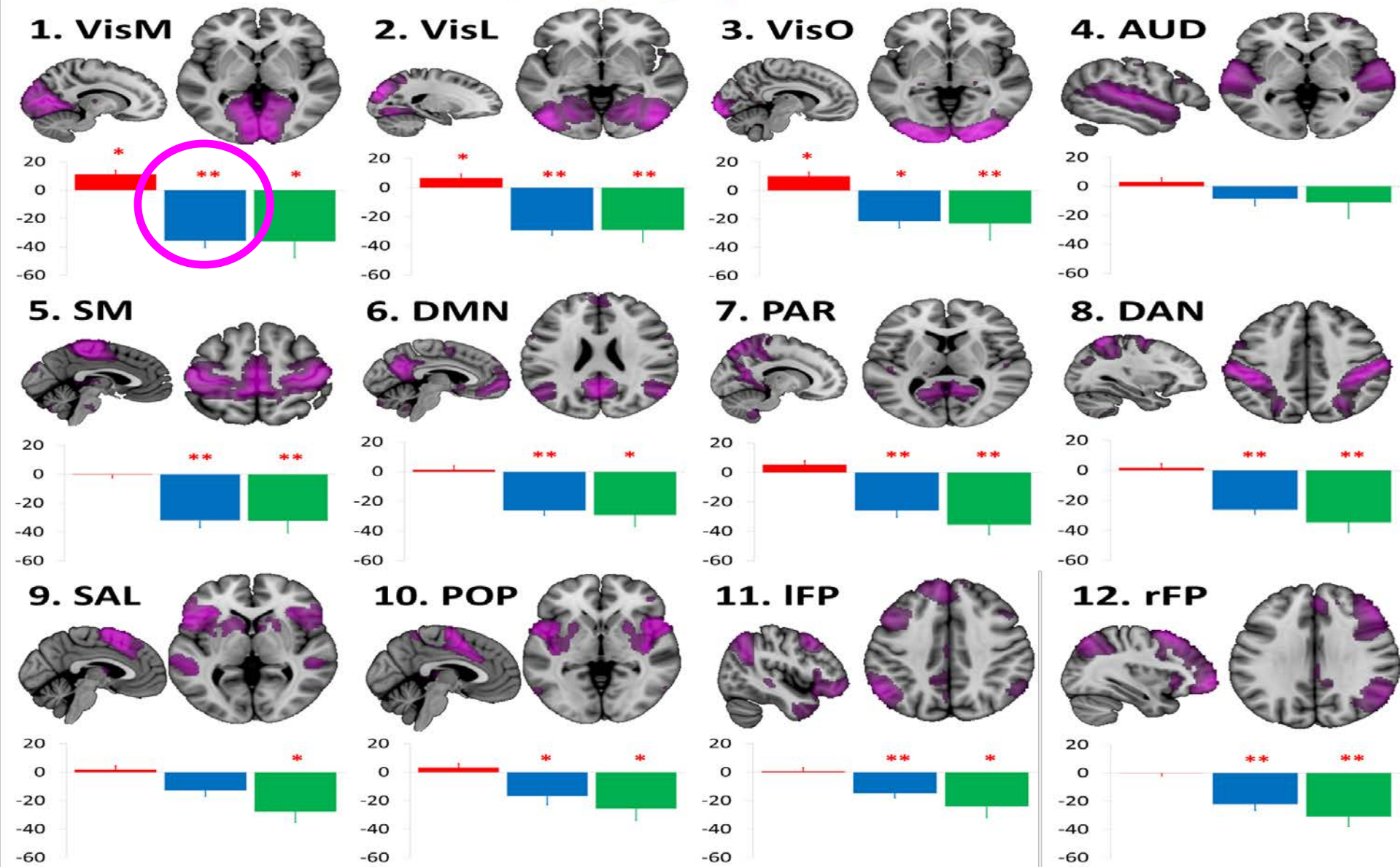


Network disintegration on LSD

a)

Intra-RSN metrics (LSD minus placebo):

CBF, **integrity**, **signal variance**

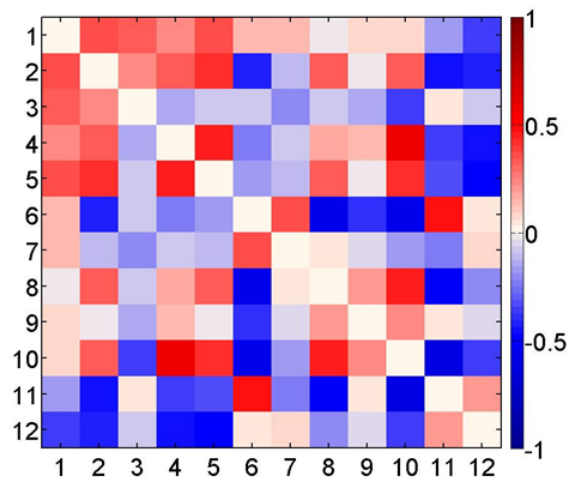


Network desegregation on LSD

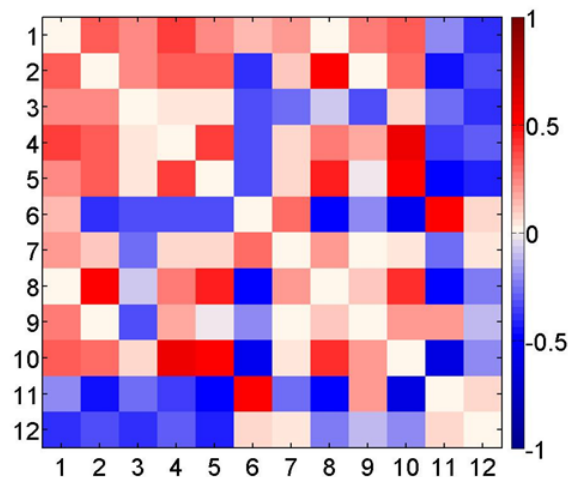
b)

Inter-RSN RSFC/segregation

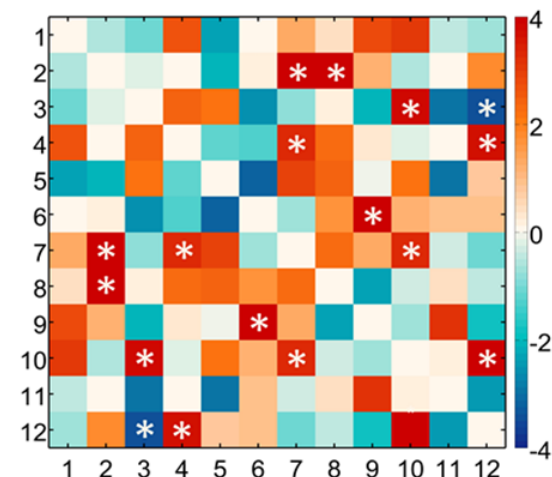
Placebo



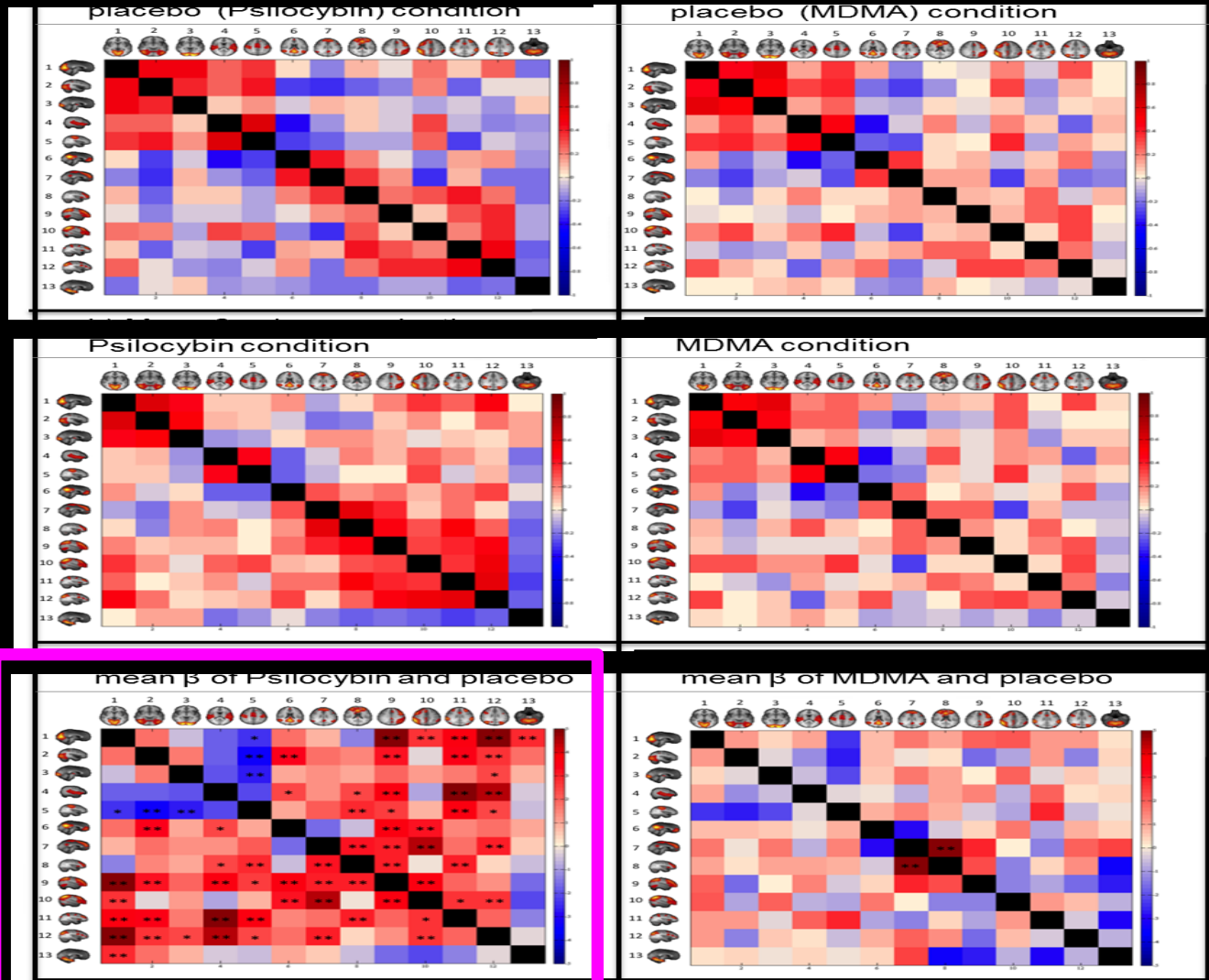
LSD



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 ↓

Psychedelic's action: Key principles

1. Network disintegration



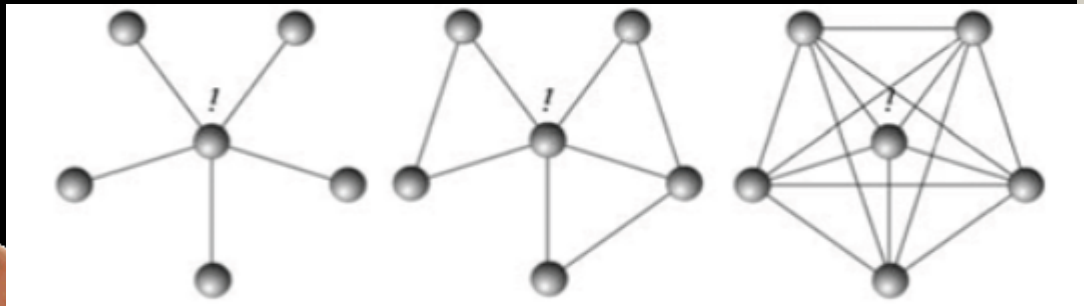
2. Network desegregation



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

Psychopharmacology (2006) 187:268–283
DOI 10.1007/s00213-006-0457-5

ORIGINAL INVESTIGATION

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

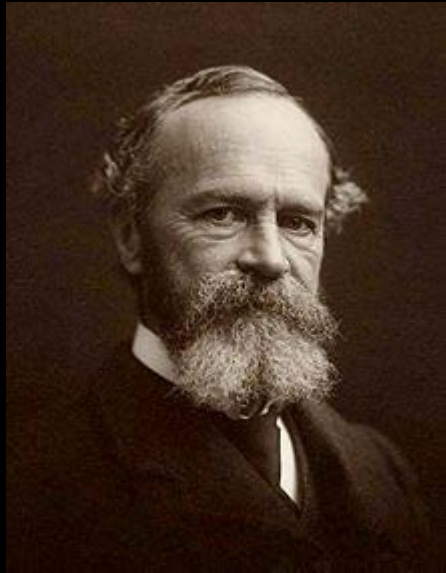
30mg psilocybin →
‘Complete mystical experience’ in 22 of 36
(Griffiths et al. 06)

*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”*

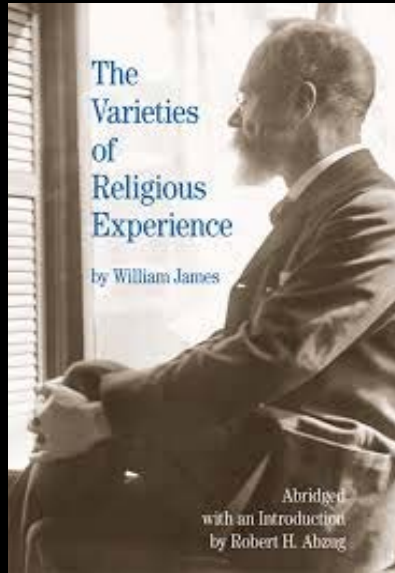
William
Wordsworth



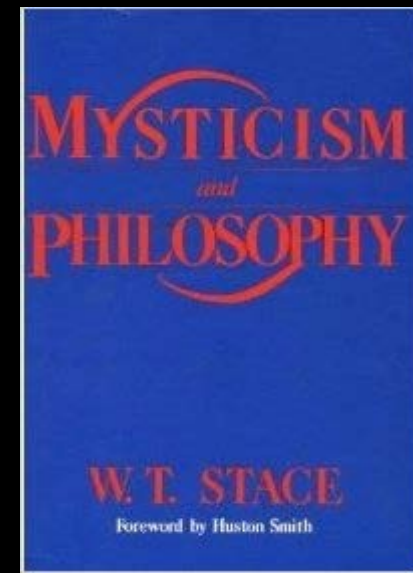
Ego-dissolution → transformative experiences ↑



William James (1842-1910)



Walter Stace (1886-1967)



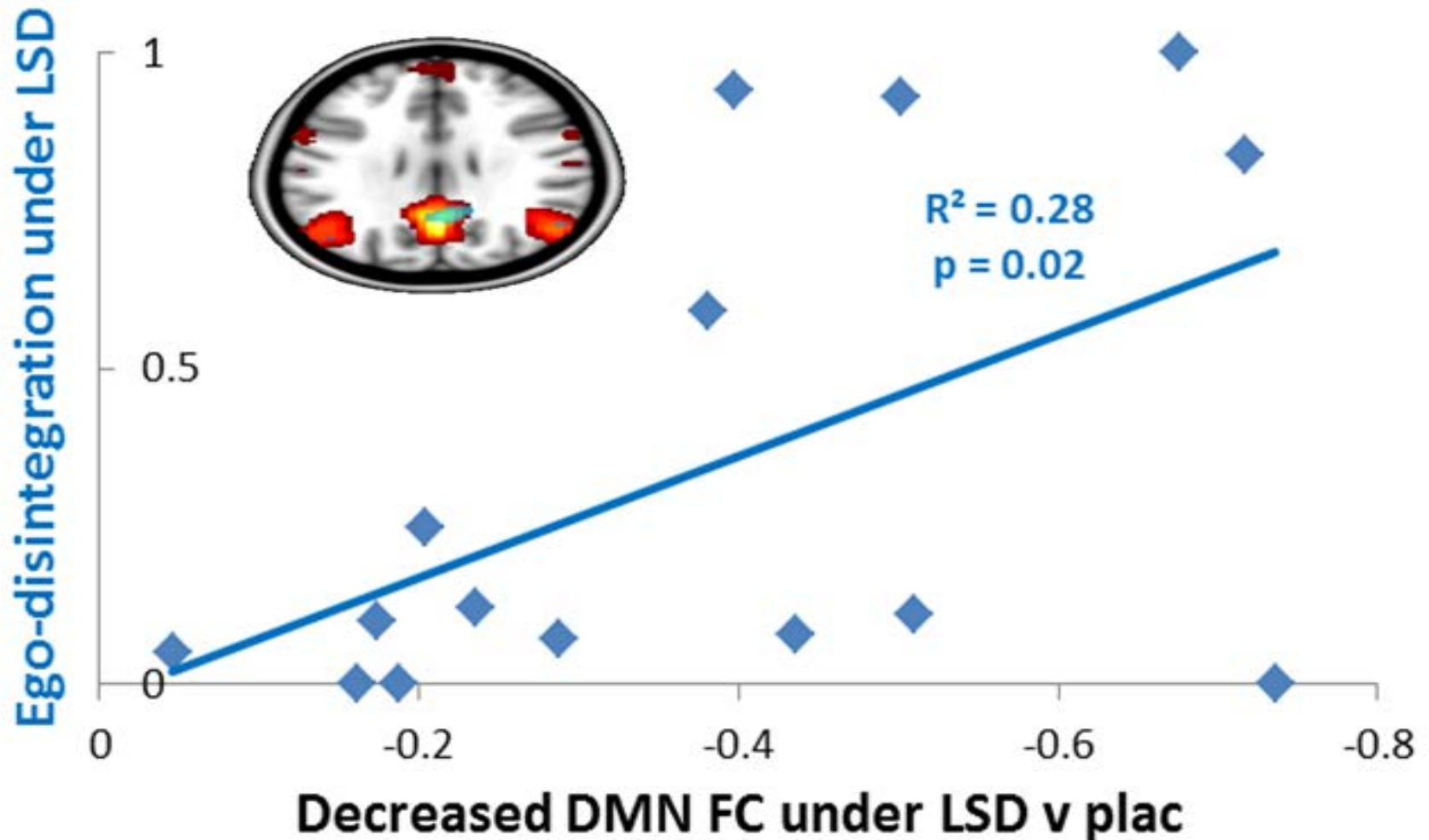
Religious/spiritual/mystical experience:

Loss of self (James)

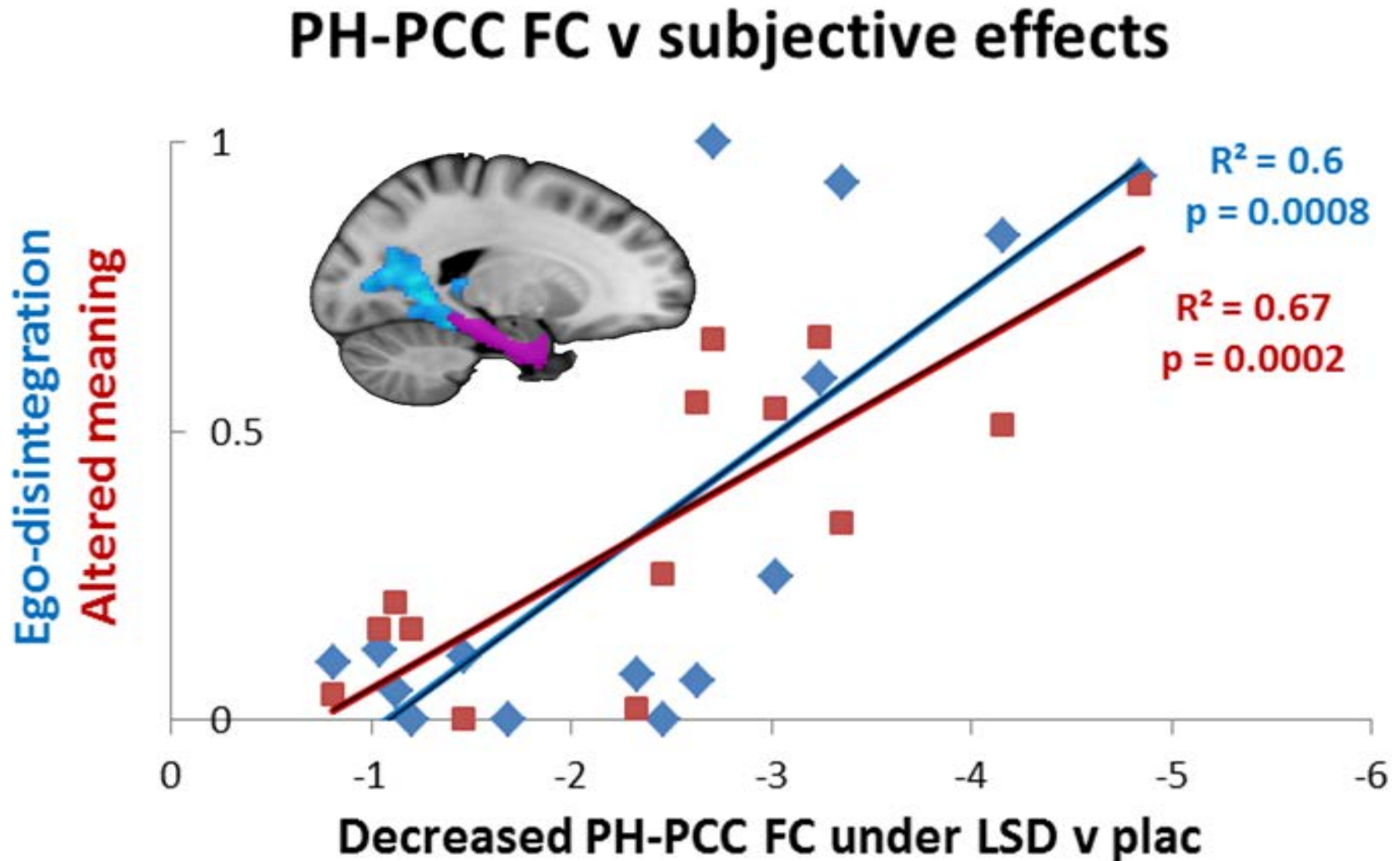
Sense of oneness (Stace)

DMN disintegration ↑
ego disintegration ↑

DMN disintegration v ego-disintegration



PH-PCC disconnection ↑ ego disintegration & altered meaning ↑



PH-PCC disconnection \uparrow psychosis \uparrow ?

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

2003

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

Clinical
Neuroscience

3: 89–97 (1995)

Schizophrenia: A Disconnection Syndrome?

1995

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

Serotonin 2A receptor stim ↓ mood ↓

- 5-HT_{2A}R ↑ in depression (e.g. Bhagwaga et al. 06)
- 5-HT depletion → 5-HT_{2A}R ↑ (Cahir et al. 07)
- 5-HT_{2A}R binding ↑ Trait neuroticism ↑ (Frokjaer et al. 2010)
- 5-HT_{2A}R binding ↑ Pessimism in depression ↑ (Meyer et al. 2003)
- 5-HT_{2A}R blockade → psilocybin-induced positive mood ↓ (Kometer et al. 12)
& MDMA ↓ (van Wel et al. 12)

Deficient 5-HT_{2A}R stimulation →
Habitual negative thinking?

Psychedelics →



← 5-HT_{2A}R stim

Psilocybin for depression



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?

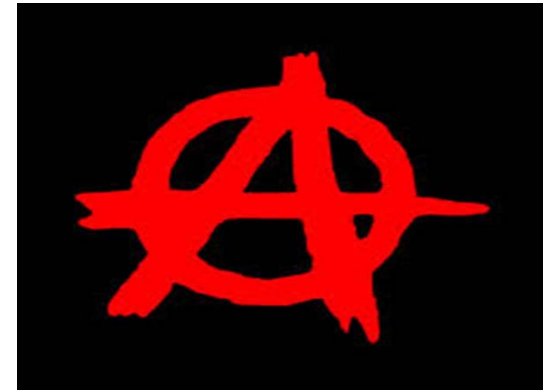
1. Network disintegration



2. Network desegregation



3. Collapse of hierarchy



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

• **Psychedelic experience \rightarrow altered political perspectives???**

A thought...



“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)

1966: Senator Bobby Kennedy defends LSD research

“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)**



Psychedelics:

an alternative to ‘bad pharma’ in psychiatry?

Thank you



Tim Williams, David Erritzoe, Mendel Kaelen, Leor Roseman, Mark Bolstridge, Ben Sessa, Suresh Muthukumuraswamy, Richard Wise, Luke Williams, Kevin Murphy, Robert Leech, Eduardo Schenberg, Neiloufar Family, Matt Wall, Val Curran, Karl Friston, Rosalyn Moran, David Nichols, Robin Tyacke, James Stone, Laurence Reed, Nadar Abbasi, Enzo Tagliazucchi, Dante Chialvo, Roland Griffiths, Katherine MacLean, Matt Johnson, Charlie Grob, Bill Richards, Jeff Guss, George Goldsmith, Ekaterina Malievskaia, Celia Morgan, Mitul Mehta, Alexander Lebedev, Pete Hellyer, Csaba Orban, John McGonigle, Remi Flechais, Michael Bloomfield, Steve Pilling, Matt Brookes, Tim Nest, Paul Expert, Giovanni Petri, James Rucker, Camilla Day, Shlomi Raz, John Evans, Peter Hobden, Wouter Droog, Yvonne Lewis, Mark Tanner, Ineke de Meer; Alison Diaper, Ann Rich, Sue Wilson, volunteers, patients and others