A Critical Lens on the Acute and Enduring Effects of Psychedelics on Brain Function, Cognition, & Emotion

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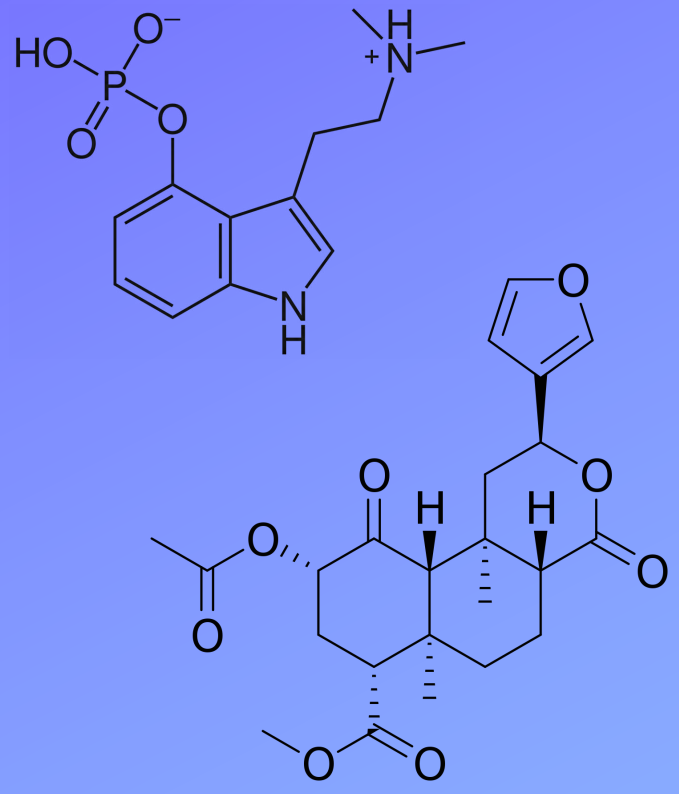

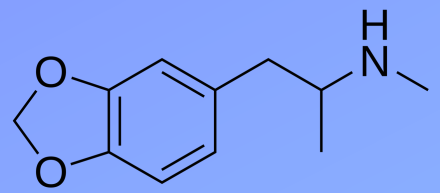

Psych

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  - Psilocybin, L
    mescaline, b
    DOI, DOM,
    MDMA (but
- The main playe
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- Have been usec
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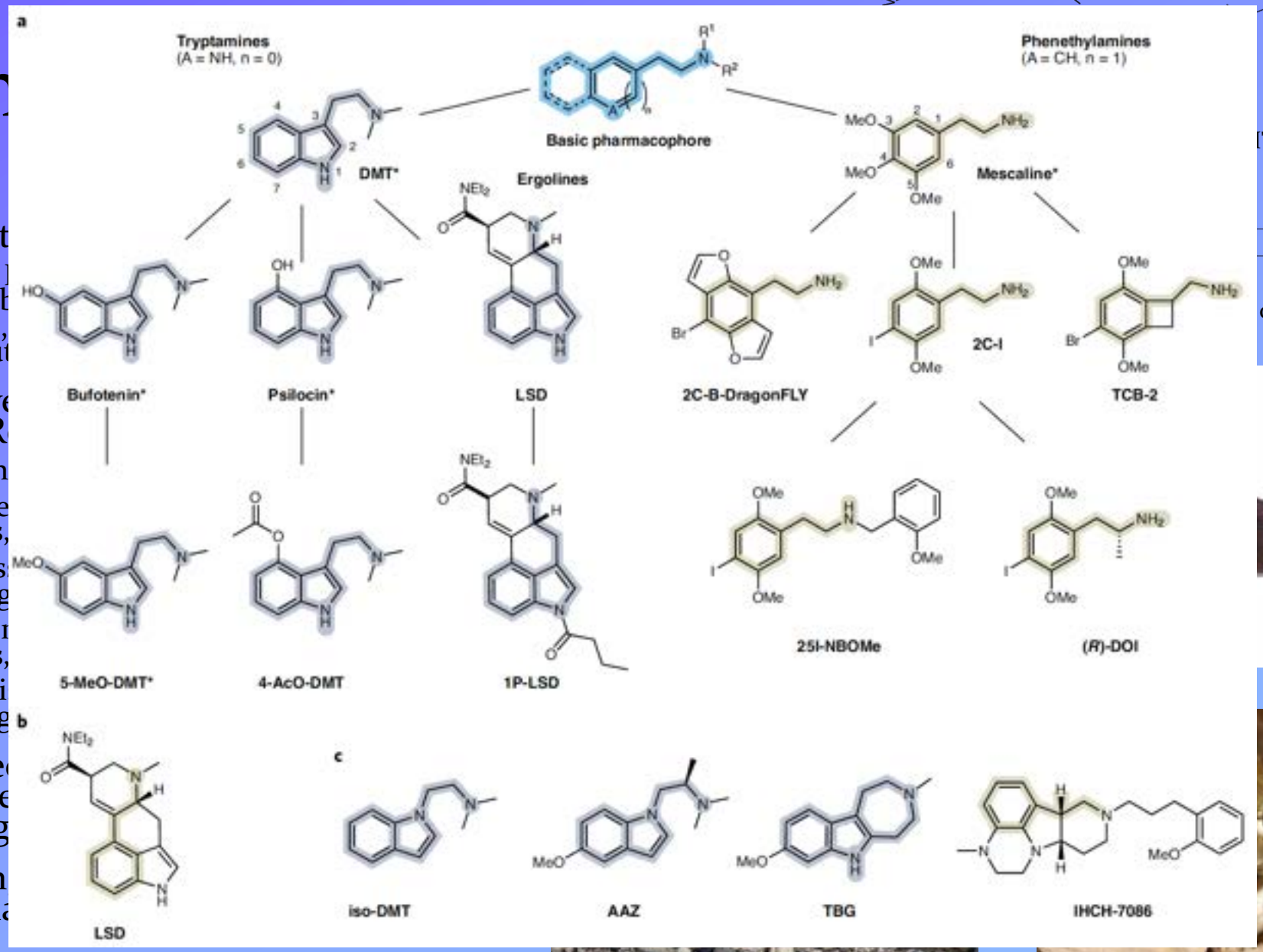
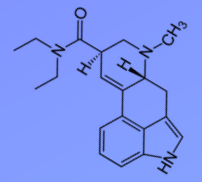
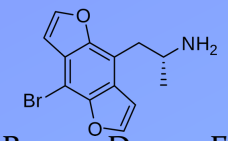




LSD



Bromo-DragonFLY

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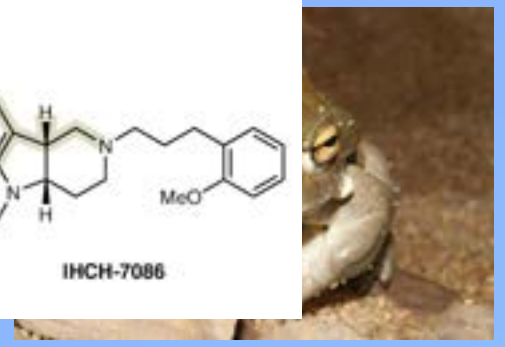

Outline

- Acute effects of psychedelics on brain function
  - Does the default mode network (DMN) have a privileged role?
- Acute effects of psychedelics on cognition
  - Episodic memory
  - Microdosing
- Enduring effects of psychedelics on brain function, emotion, and cognition
  - Healthy adult study
  - Depression study

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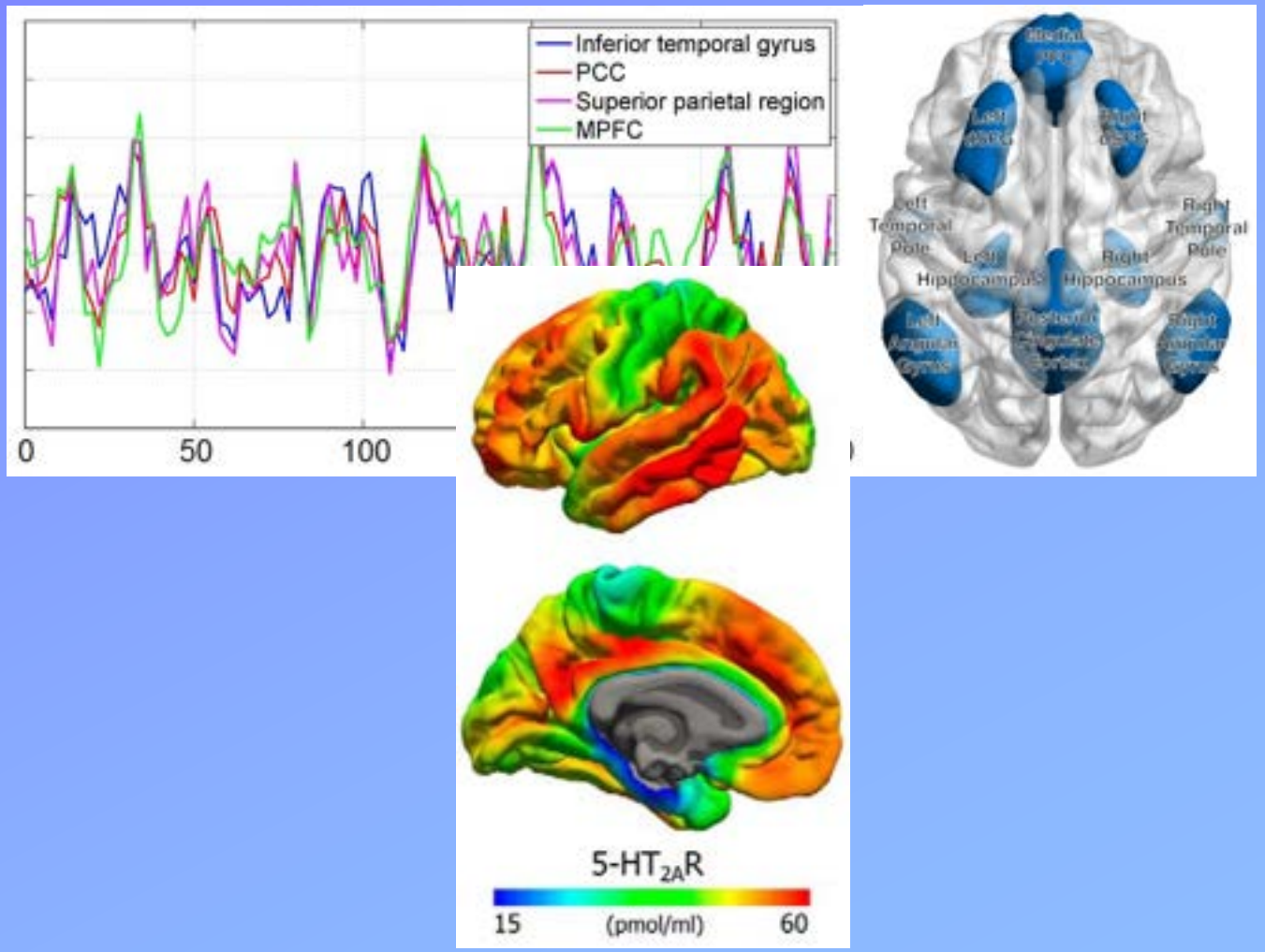
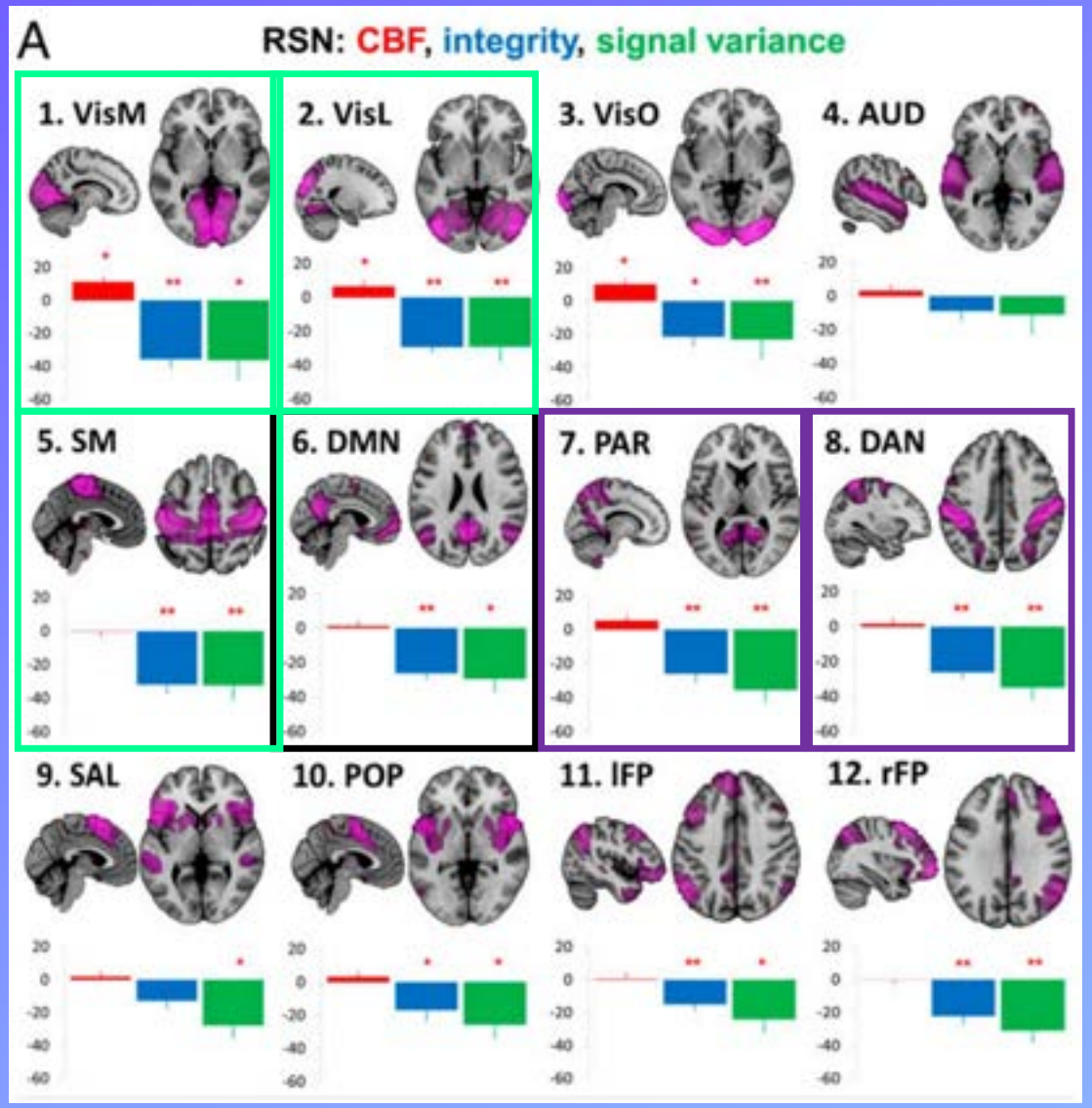
The Default Mode Network Narrative

- Static functional connectivity (sFC) - Strength of association between activity of two or more regions over time.
- Psilocybin decreased task-free activity and sFC within DMN (Carhart-Harris et al., 2012).
  - Replicated with ayahuasca (Palhano-Fontes et al., 2015), LSD (Carhart-Harris et al., 2016; Müller et al., 2018), and psilocybin (Mason et al., 2020).
  - Correlated with "ego dissolution" in one study (Carhart-Harris et al., 2016).
- Default mode network (DMN) involved in self-referential processing and thus, has been proposed to be the "ego."
- RElaxed Beliefs Under pSychedelics (REBUS) posits the DMN at the top of the brain's hierarchy.
  - Hierarchy collapses under psychedelics leading to "entropy."
  - Larger effects in higher-level networks (i.e., not sensory).
- Michael Pollan popularized this narrative to the broader public.



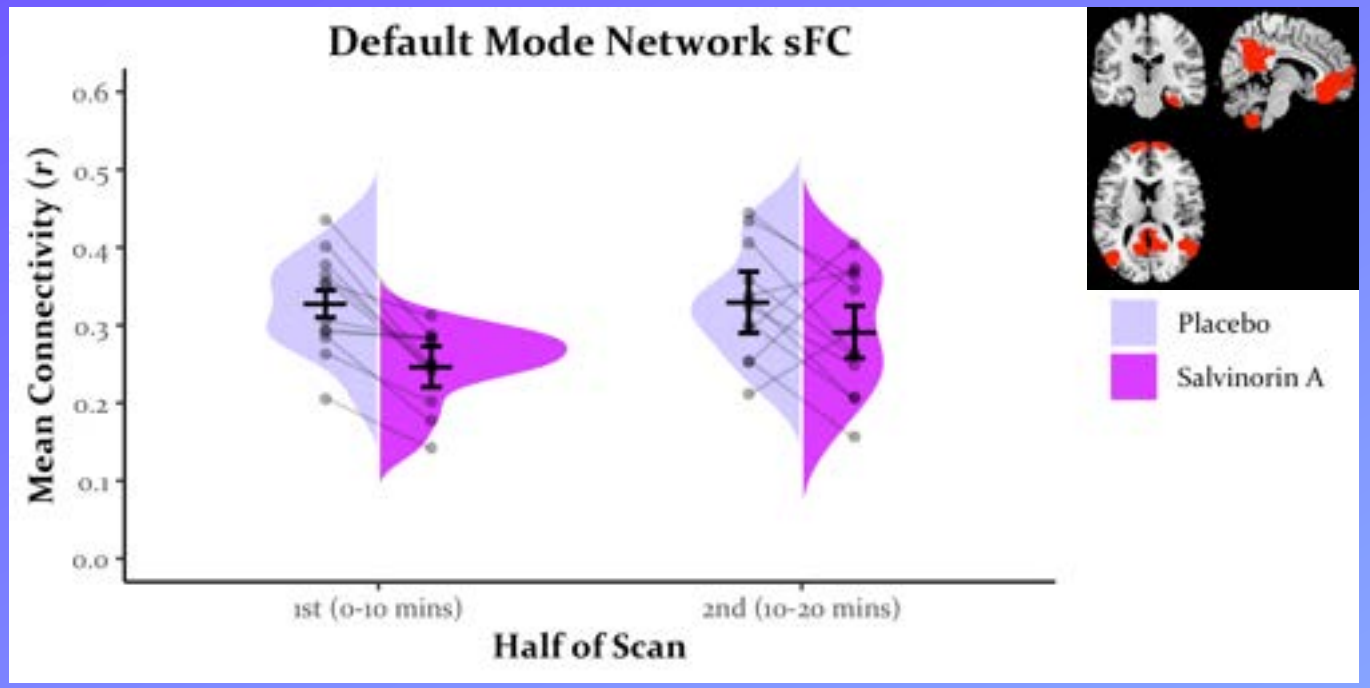
It wasn't always only about the DMN…

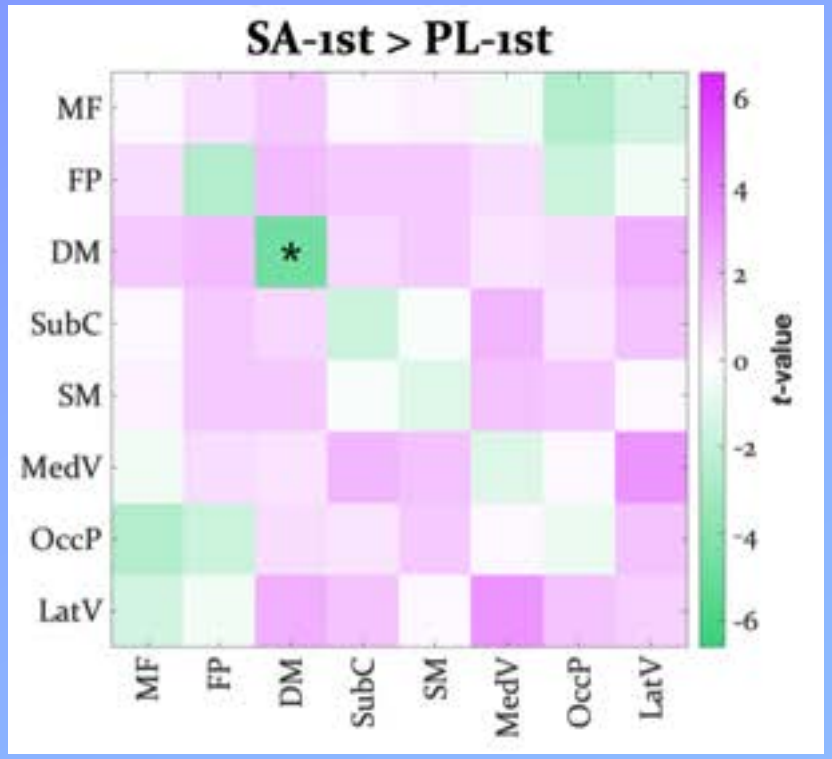
- Correlations with ego dissolution did not replicate (Müller et al., 2018).
  - Loads of activation patterns correlate with ego dissolution (Millière et al., 2018).
- DMN involved in more than the self (e.g., episodic memory, theory of mind, future simulation).
- Increases and decreases in activity found within and outside of the DMN (Daumann et al., 2008, 2010; Gouzoulis-Mayfrank, 1999; Hermle et al., 1992; Vollenweider, 1997, 1999).
- Stronger decreases in sFC outside of DMN (Carhart-Harris et al., 2016; Mason et al., 2020; Müller et al., 2018).



◆ **LSD-Induced Entropic Brain Activity** ◆

	Network		
N	Description	*T* Drug	*P* Drug
1	**Secondary Visual**	4.698	<0.001***
2	**Primary Visual**	6.019	<0.001***
3	**Superior Sensorimotor**	6.209	<0.001***
4	Inferior Sensorimotor	1.238	0.219
5	**Superior Parietal**	4.961	<0.001***
6	**Posterior Sensorimotor**	5.971	<0.001***
7	Posterior Salience	1.651	0.102
8	**Anterior Salience**	4.020	<0.001***
9	Anterior MTL	−0.710	0.479
10	Orbitofrontal	0.651	0.517
11	**Precuneus**	6.068	<0.001***
12	**Inferior Frontoparietal**	6.401	<0.001***
13	**Superior Frontoparietal**	5.171	<0.001***
14	Auditory	0.511	0.610
15	**Hippocampal**	2.531	0.013*
16	**Default Mode**	3.594	0.001**
17	Frontotemporal	1.560	0.122





Doss et al. (2020), *Scientific Reports*

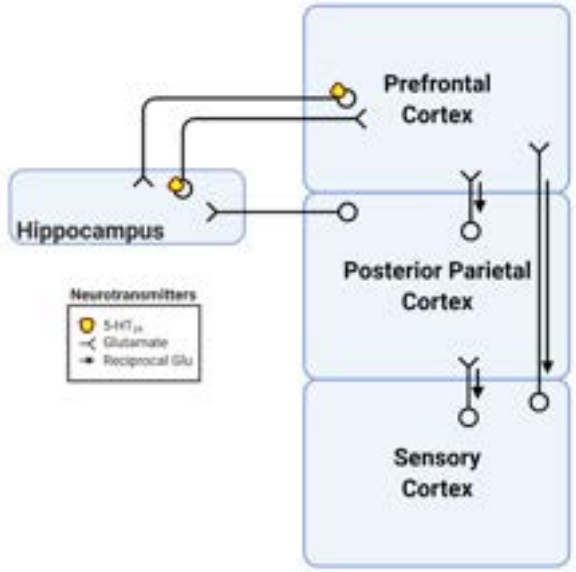
Are reductions in functional connectivity within the DMN specific to hallucinogens?

- Ketamine - decreases (Bonhomme et al., 2016; Zacharias et al., 2020), no effect (Mueller et al., 2018; Niesters et al., 2012), increases (Fleming et al., 2019).
- THC - decreases (Wall et al., 2019)
- Amphetamine - decreases (Schrantee et al., 2016)
- Alcohol - decreases (Weber et al., 2014)
- SSRI - decreases (Klaassens et al., 2015)

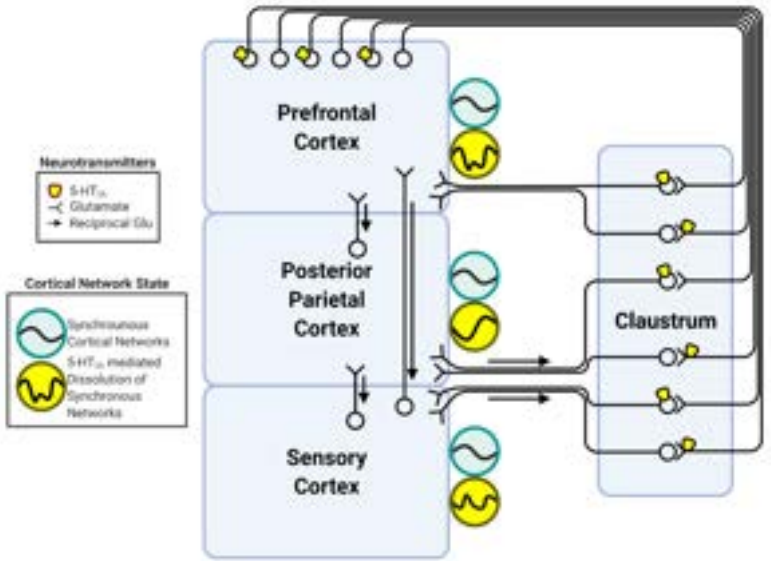
Unconstrained cognition under “resting state” conditions is likely an issue…

Other Models of Psychedelic Drug Action (Doss et al., 2022, *Brain*)

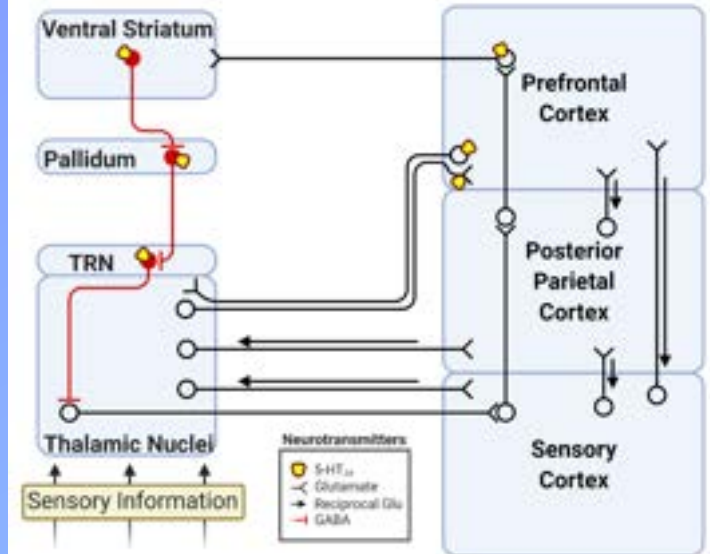
REBUS



Cortico-Claustro-Cortical (CCC)



Cortico-Strital-Thalamo-Cortical (CSTC)



Also need **1) DMN-dependent behaviors** (e.g., self-referential processing, episodic memory, and theory of mind) and **2) causal manipulations** (e.g., TMS, lesion patients, and animal models).

Michael Pollan
@michaelpollan

A revisionist take on the neuroscience of psychedelic experience: 5 Questions for Manoj Doss - by jane c. hu - The Microdose

themicrodose.substack.com
5 Questions for Manoj Doss
The Microdose talks to Doss about the neuroscience of mind-altering drugs.

Manoj Doss not exist
@ManojDoss

There you have it. The man himself said it.

> **Robin Carhart-Harris** @RCarhartHarris · Oct 30, 2020
> Replying to @MGirnNeuro and @michaelpollan
> Good vid. Narratives have been too DMN centric. “Shutting off” DMN is worst example. Correlations with DMN ‘disintegration’ & ED are likely nonspecific but not wrong as such. Reset thing is an extrapolation. It’s true.

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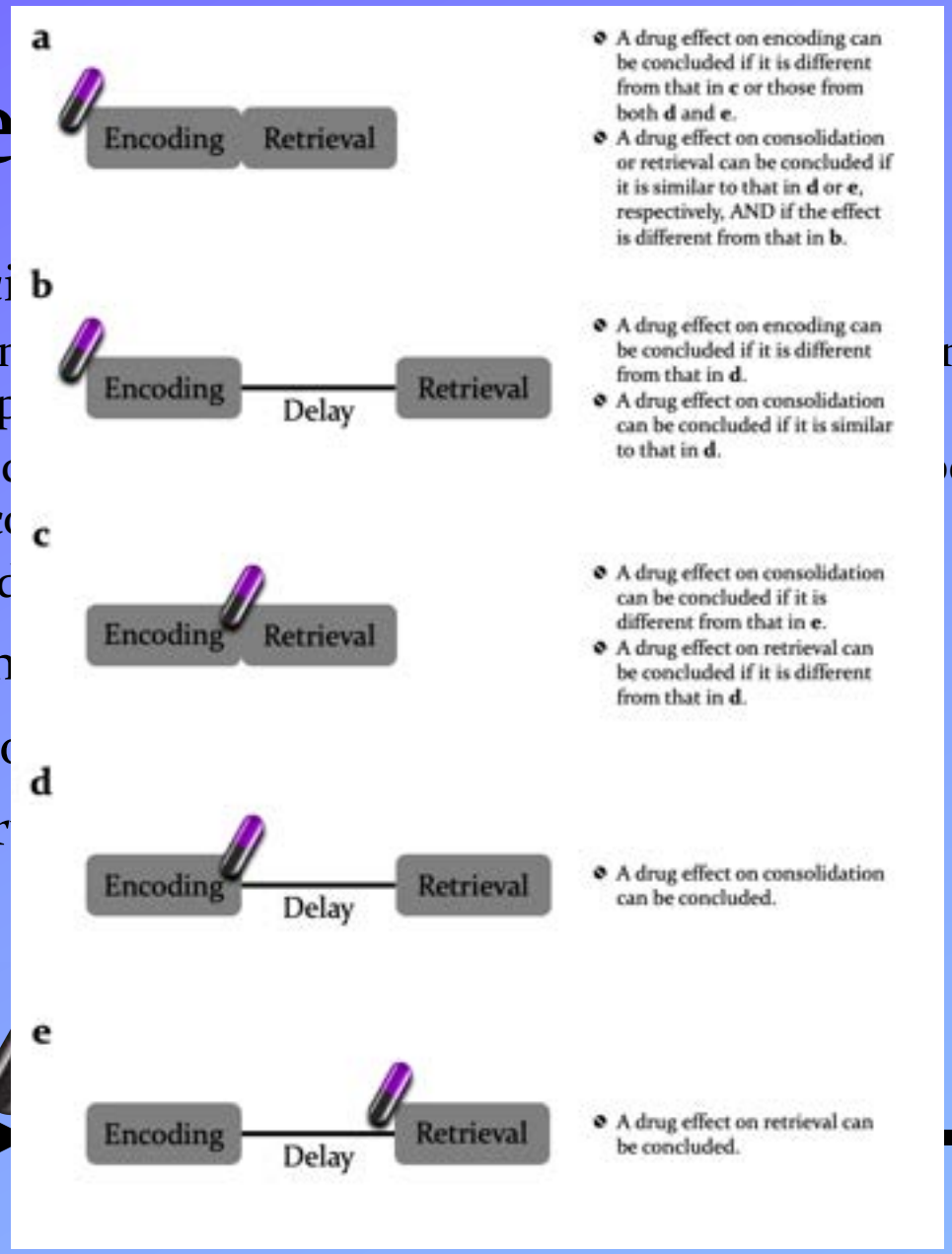
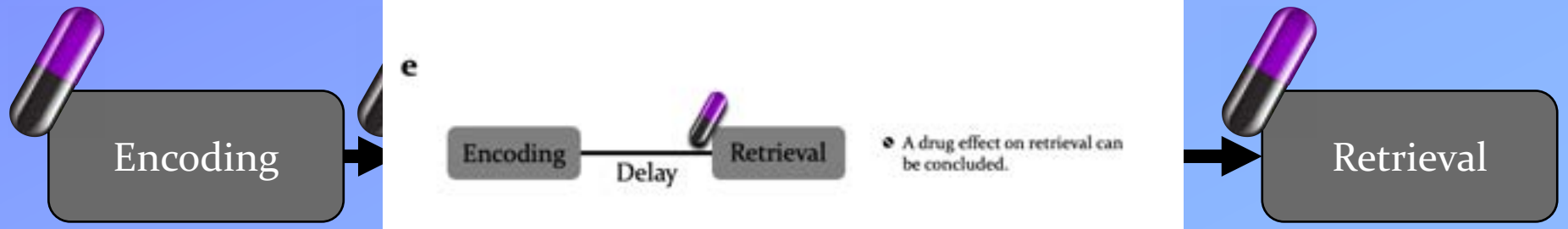
Psychedelics and Cognition

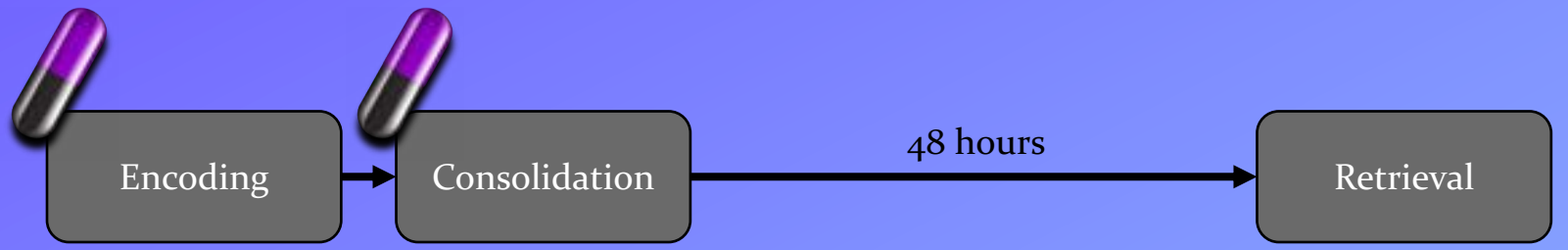
- Psilocybin enhances semantic priming (Spitzer et al., 1994).
- *R*-MDEA enhances the "pop-out" effect (Spitzer et al. 2001).
- Psilocybin impairs high level motion perception (Carter et al., 2004).
- Psilocybin impairs time perception (Wittman et al., 2007; Wackermann et al., 2008).
- Psilocybin impairs inhibitory processes (Quednow et al., 2012; Gouzoulis-Mayfrank et al., 2006)
- Psilocybin increases threshold for detecting fearful faces (Schmidt et al., 2013).
- Psilocybin impairs psychomotor function (Barrett et al., 2018).
- LSD reduces cognitive flexibility (Pokorny et al., 2019).
- Psilocybin and LSD impair WM (Barrett et al., 2018, Pokorny et al., 2019, Wittmann et al., 2007).
- Psilocybin and MDMA impaired some measures of episodic memory (Barrett et al., 2018; Doss et al., 2018).

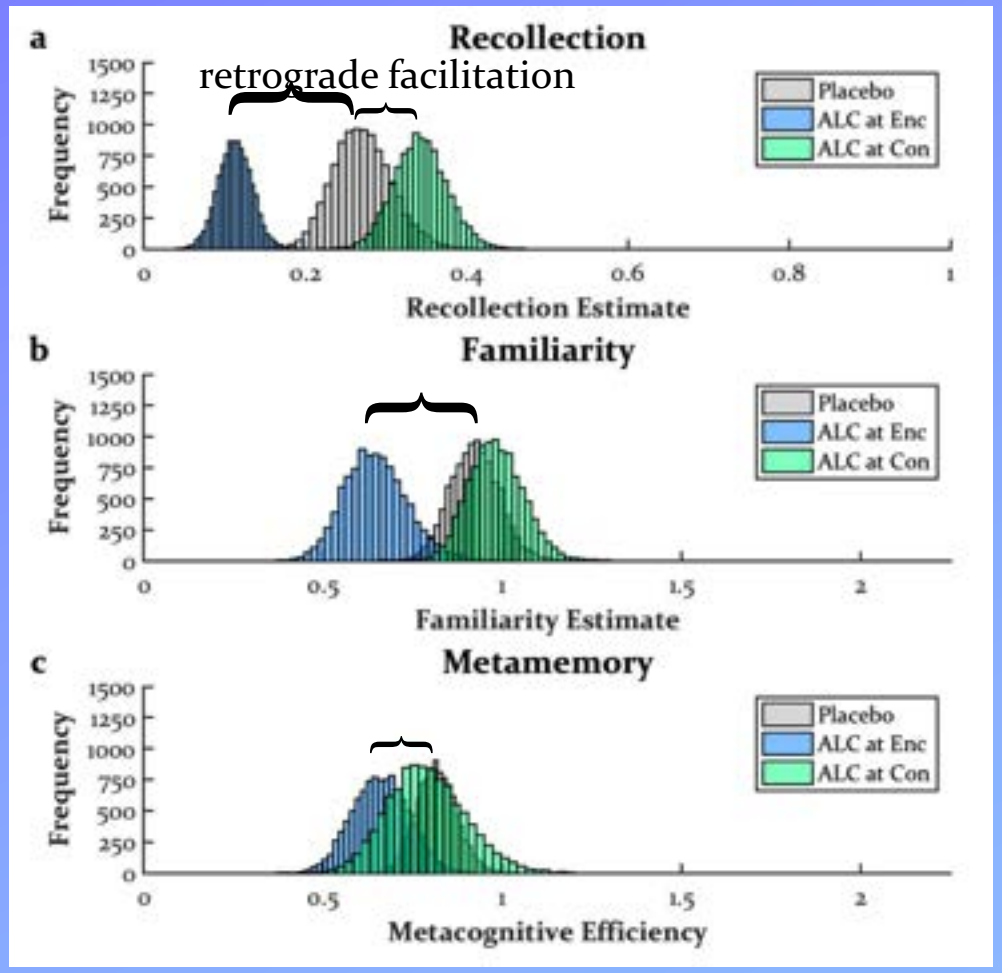
Episodic Me

- The conscious reexperienci time travel" –Endel Tulving)
  - **Recollection** - Hippocar rom an event like where and when oneself was in the p
  - **Familiarity** - Cortically-c een experienced without specific details ("noetic c
  - **Metamemory** - Knowlec
- **Encoding** - studying/learn
- **Consolidation** - post-enc
- **Retrieval** - testing memor

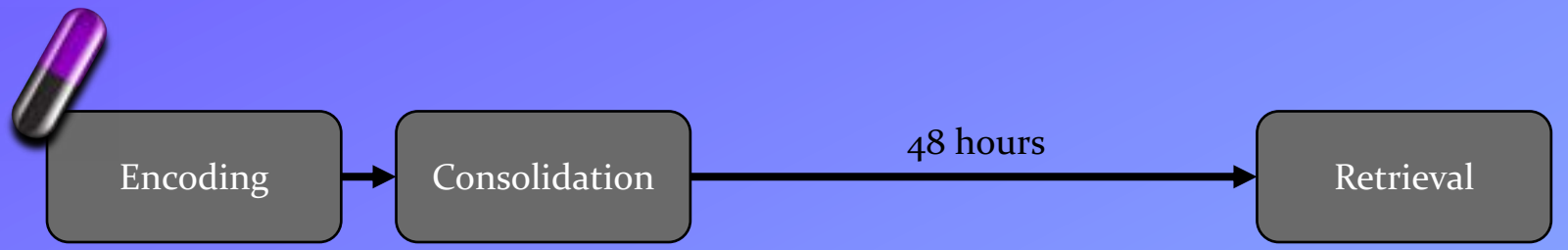


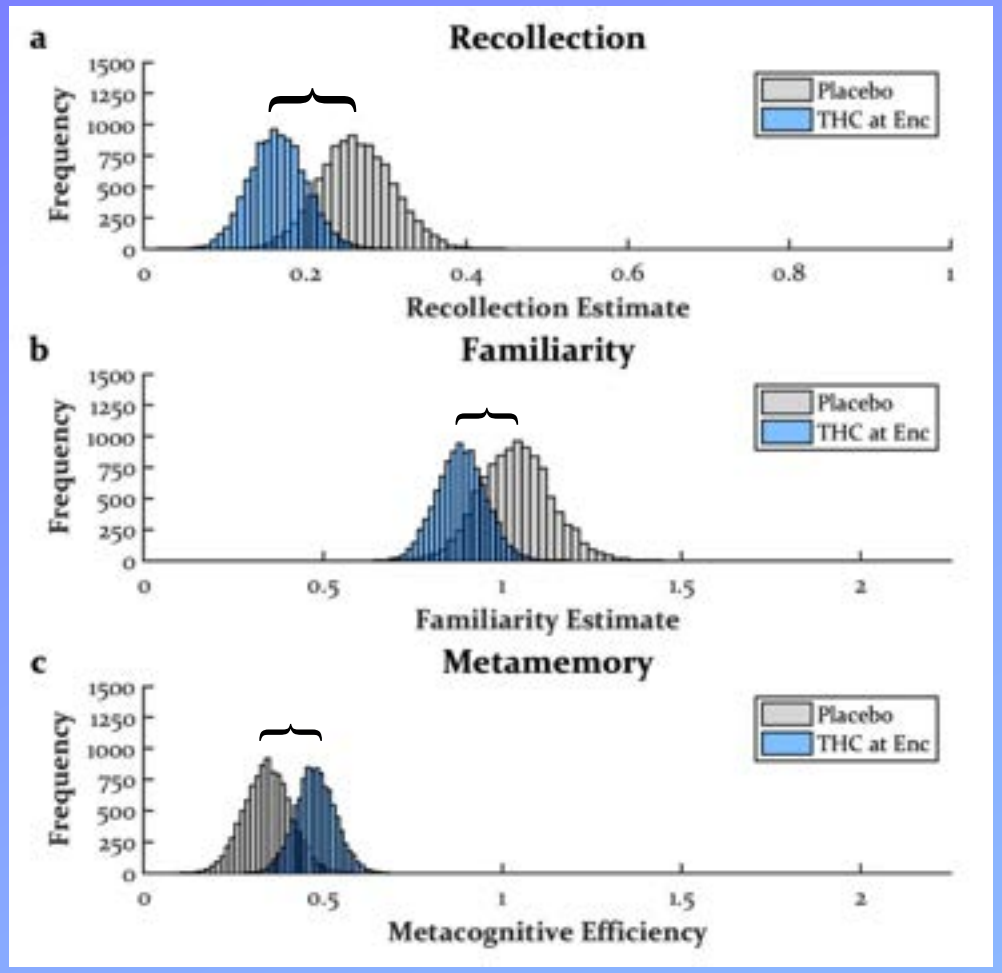






Doss et al. (in review)





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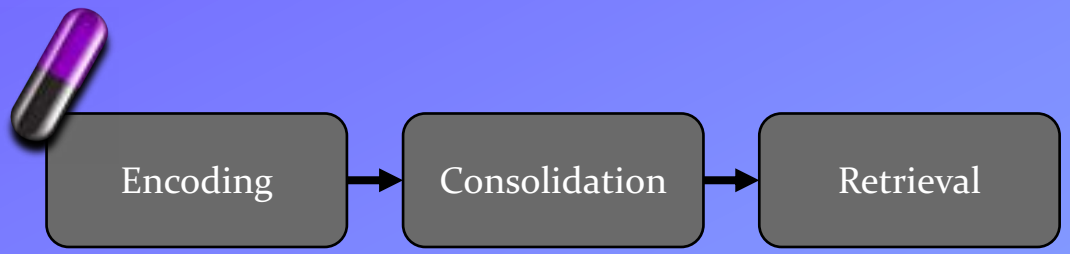

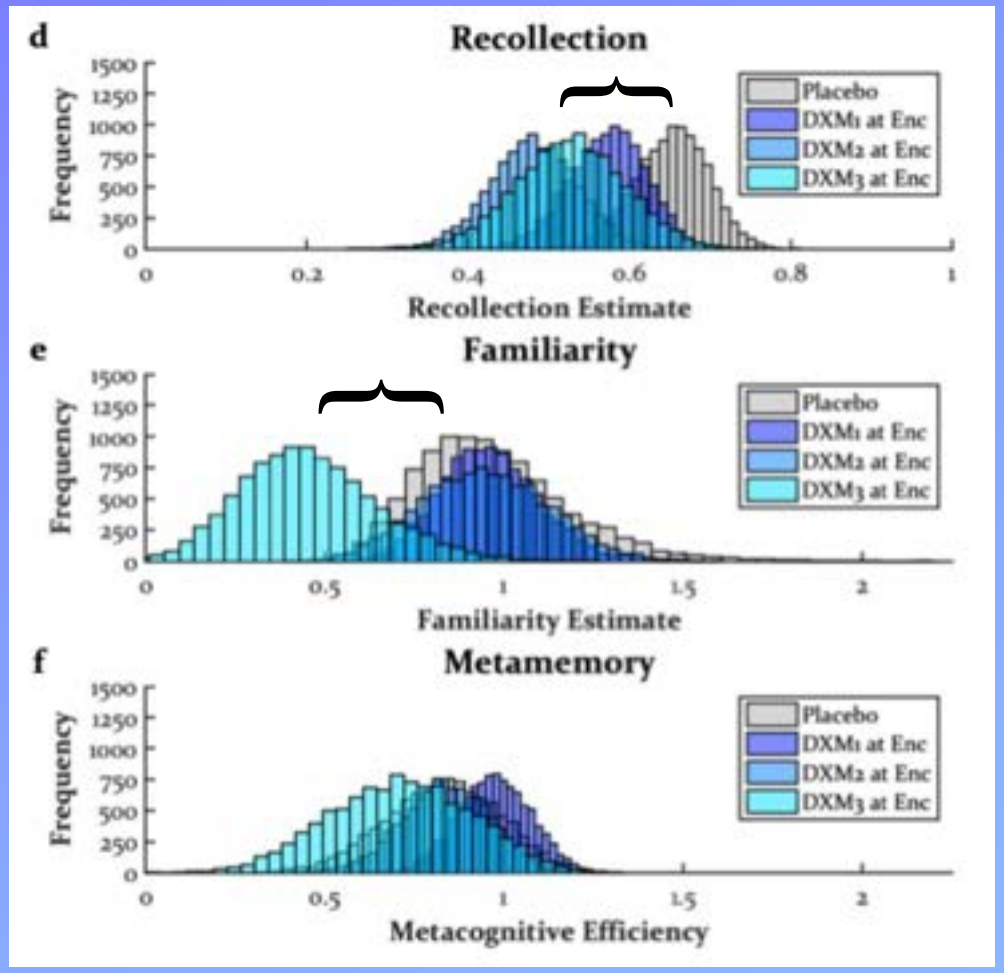

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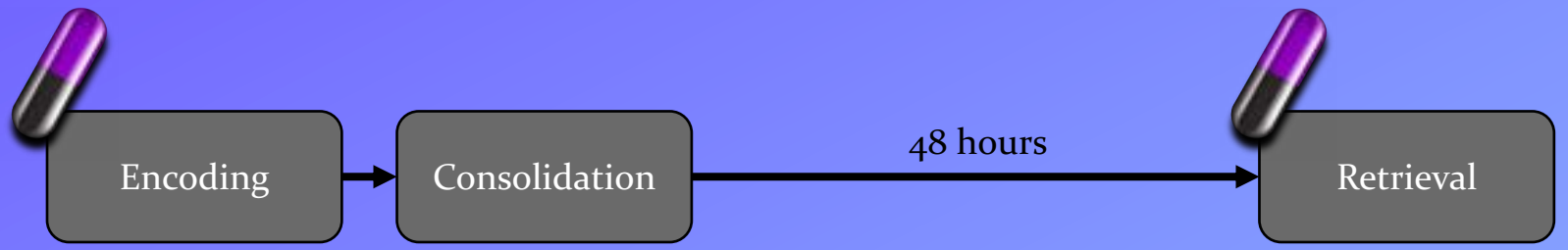

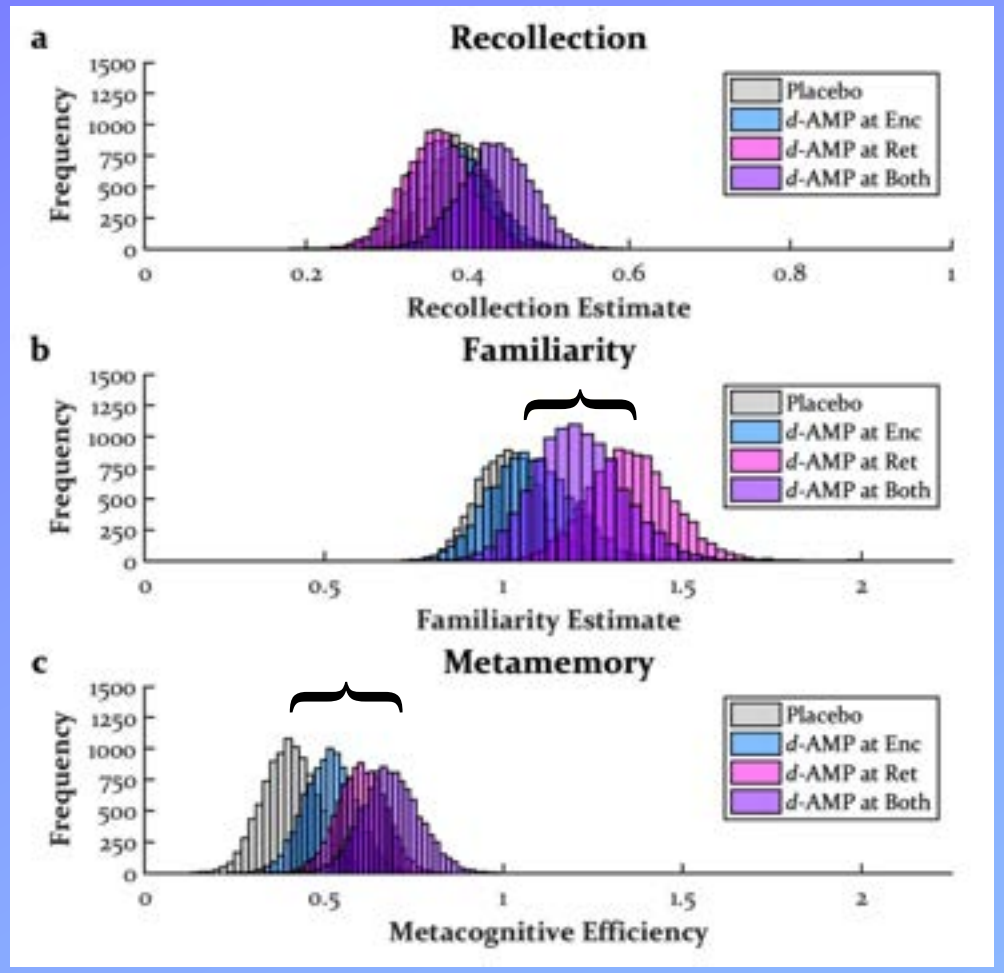

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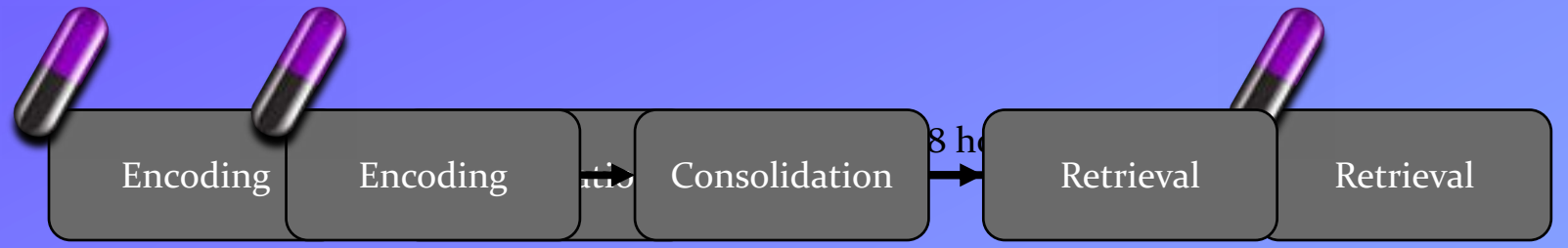
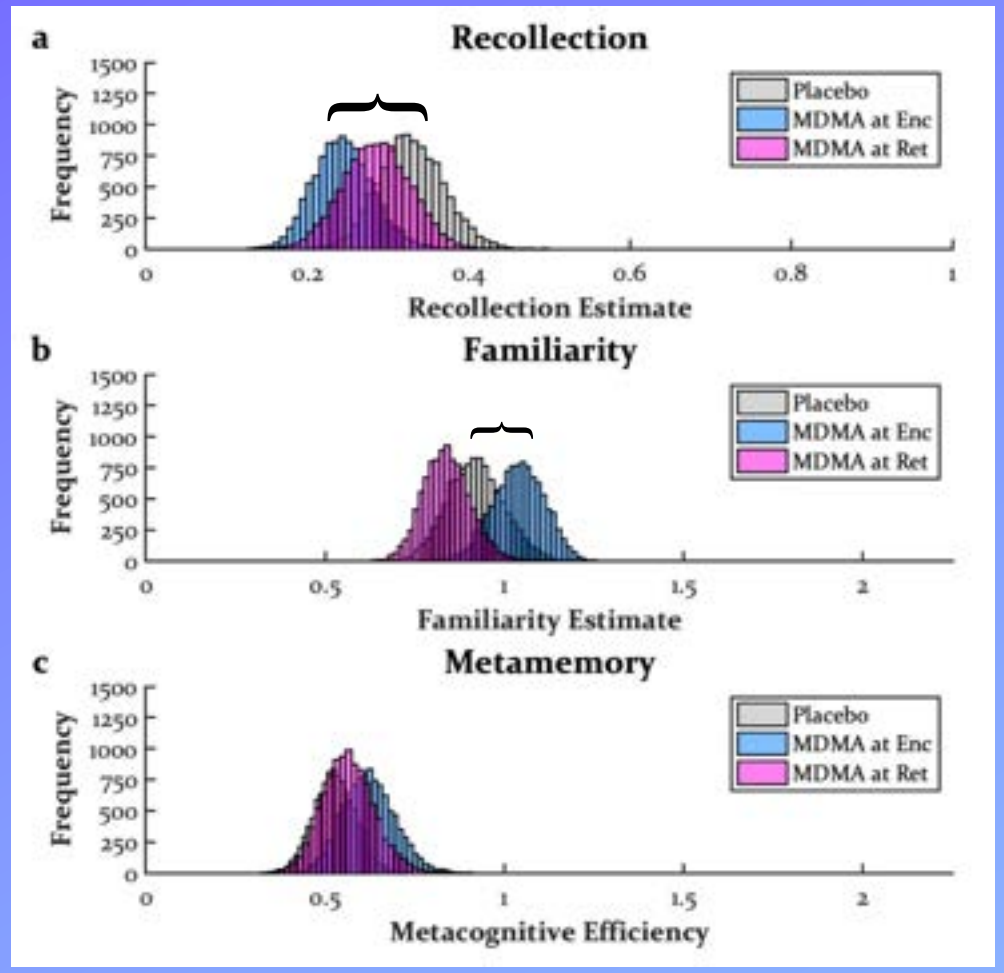
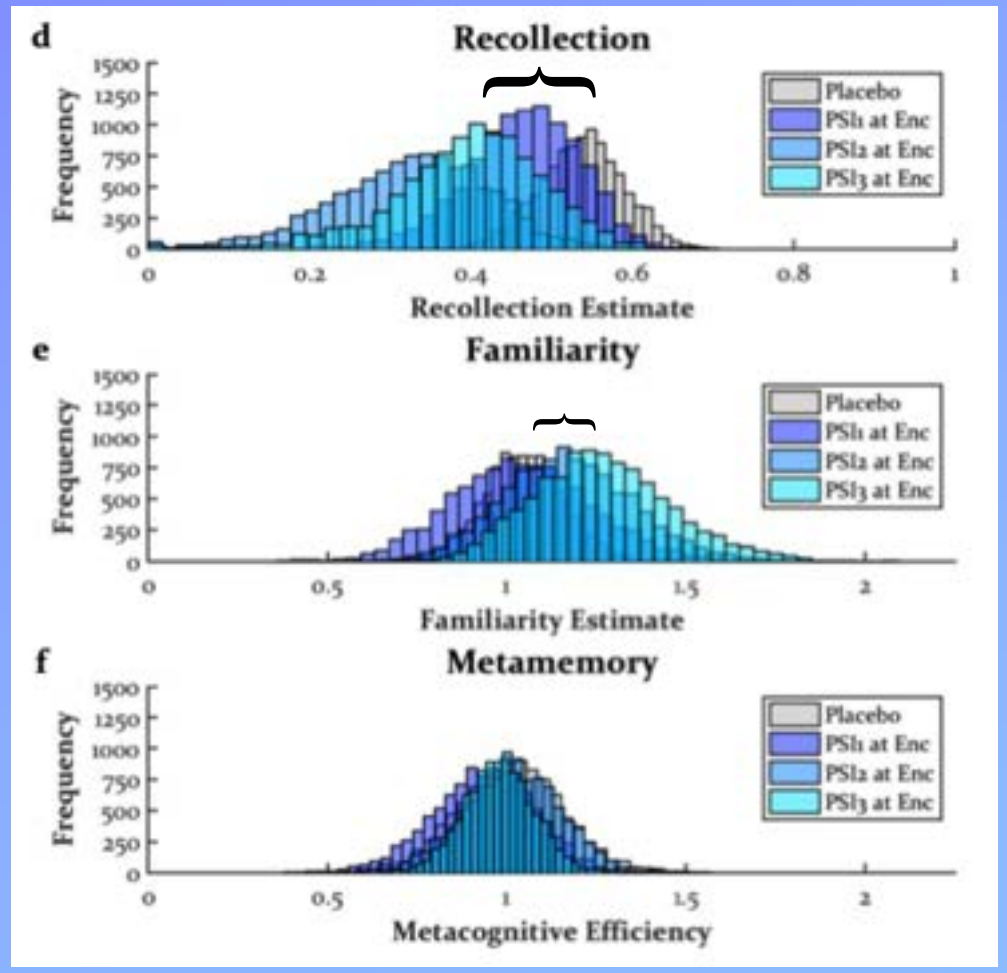






Doss et al. (in review)

Why are these effects on episodic memory interesting? The good…

- Ego dissolution ~ disruption of autonoetic consciousness (experience of recollection)
- Noetic quality (undeniable sense of knowing) ~ enhancement of noetic consciousness (experience of familiarity)
- Computationally, recollection involves threshold processing and familiarity involves graded processing.
  - Other "thresholds" break down (like self and other) and more continuous form of information processing facilitated ("oneness").
    - Perhaps related to "flattening" of energy landscape proposed by REBUS.
- Cortex is a slow learner, so encoding new memories into the cortex may disrupt maladaptive "crystallized" memories.
  - Perhaps related to increased cortical plasticity (Inserra et al., 2021).

Why are these effects on episodic memory interesting? The less good…

- When recollection fails and familiarity is high, *déjà vu* (Cleary et al., 2012), feelings of premonition (Cleary & Claxton, 2018), *presque vu* (illusory insight; Kostic et al., 2015) can occur.
- No evidence that metacognition improves under psychedelics.
- Feelings of insight can be misattributed to unrelated ideas (Laukkonen et al., 2022).
- Familiarity unconstrained by recollection can be misattributed to unrelated stimuli (e.g., Doss et al., 2016; 2018; 2020; Roediger & McDermott, 1995).
- Most drugs increase false memories upon retrieval (Doss et al., in review).
  - Psychedelics enhance mental imagery and suggestibility.
  - Freudian narratives of repressed memories are not supported by memory researchers (Otgaar et al., 2021).
- Enhanced feelings of insight (encoding effect) + enhanced memory distortion (retrieval effect) = great recipe for false memories and delusions.
- Memory distortion may be good for rewriting maladaptive memories (i.e., reconsolidation).
- MDMA, specifically, induces stereotyped lateral eye movements like EMDR.
  - Lateral (but not vertical) eye movements associated with enhanced memory retrieval and distortion.
  - Saccades drive hippocampal theta phase resetting associated with memory formation/plasticity.

Microdosing

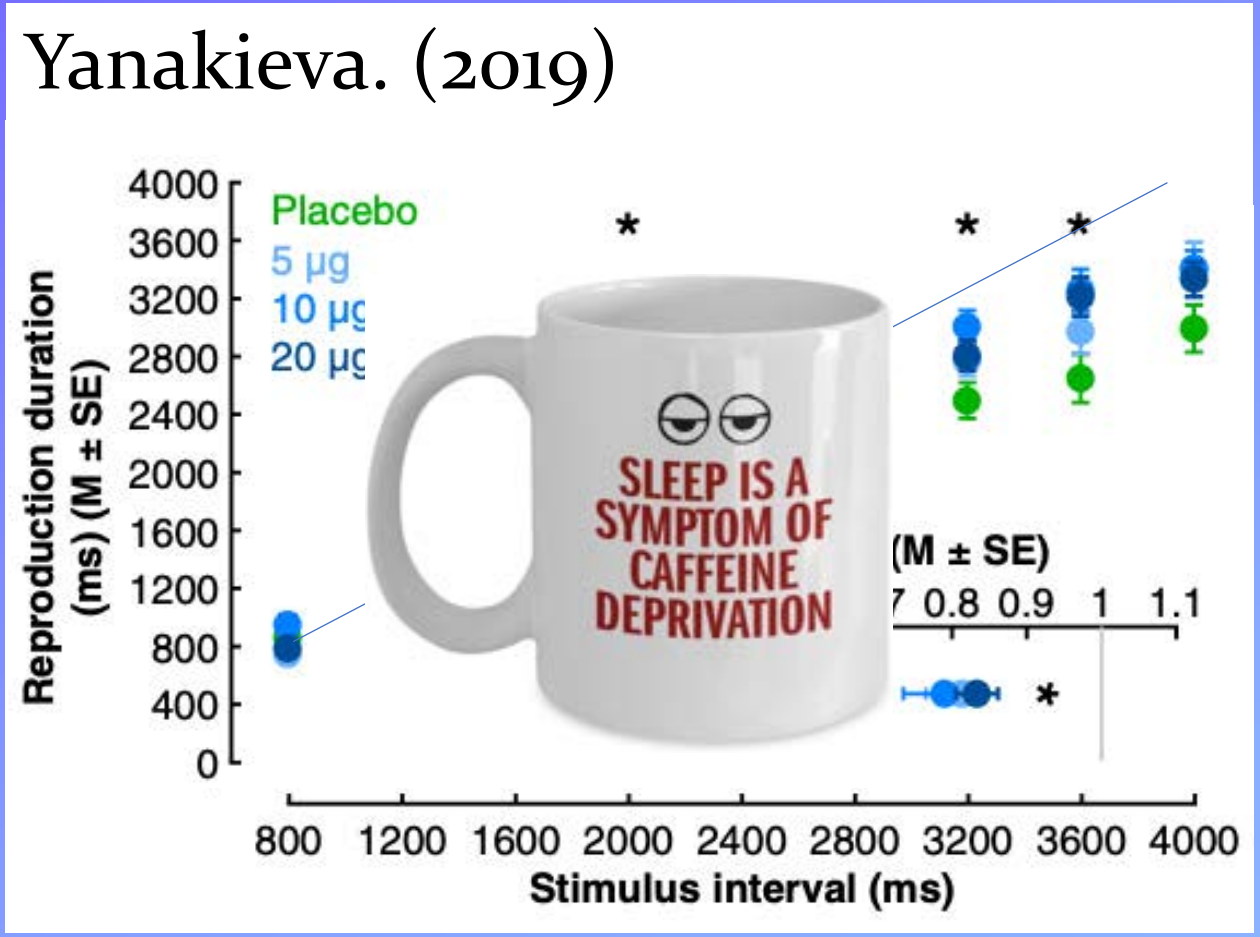
- ≈1/10 of a standard dose
  - e.g., 10 µg of LSD, 1.5 mg of psilocybin, .2 g of dried mushrooms
  - 1/4 of a standard dose might be considered a “low dose”
- In the wild, many practices involve variable days on and days off.
  - e.g., 1 day on, 2 days off
- Microdoses of LSD increase stimulant-like effects and positive affect (Bershad et al., 2019; de Wit et al., 2022; Family et al., 2020; Hutten et al., 2020; Murray et al., 2021).
  - But also increase anxiety.
  - Repeated dosing did not improve mood off drug (de Wit et al., 2022; Family et al., 2020).
- Placebo effects on mood with self-blinding (Szigeti et al., 2021).
- Psychedelics stimulate 5-HT_{2B} receptors
  - Associated with cardiac toxicity.

Effects of Microdosing on Cognition

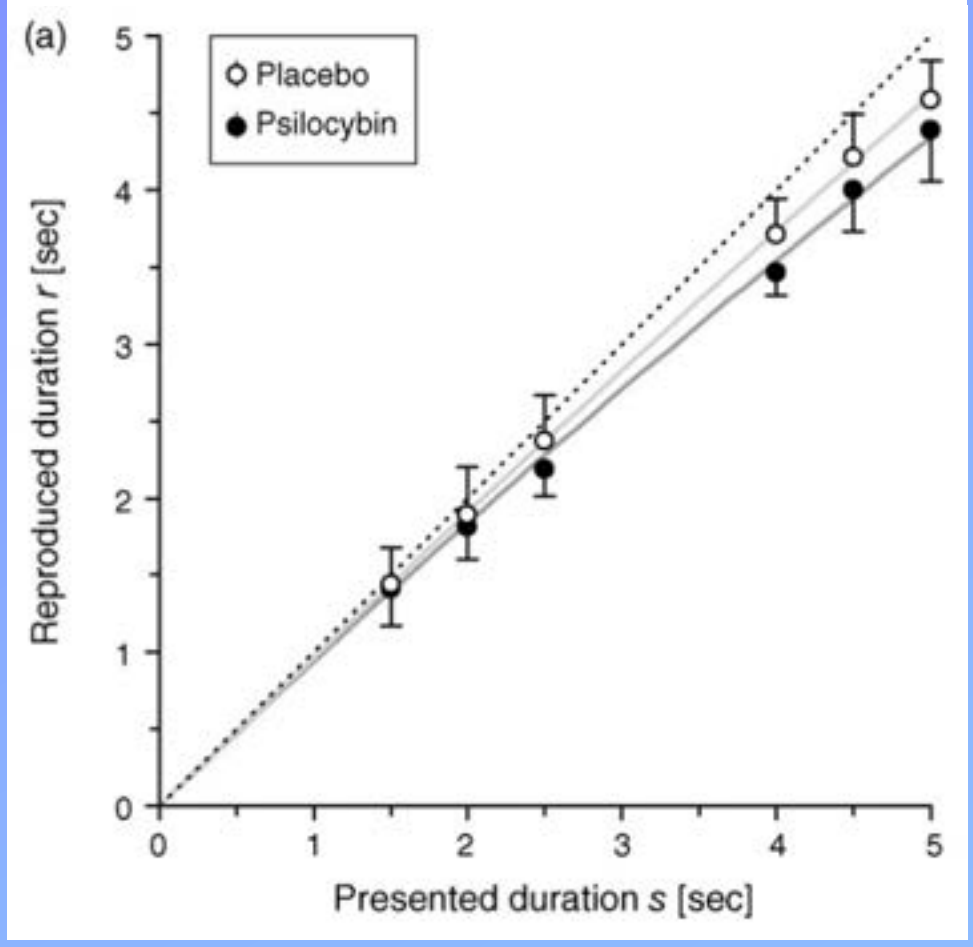
- LSD did not impact WM, emotional processing, social exclusion, or convergent thinking (Bershad et al., 2019).
- 4 microdoses of LSD did not impact WM, emotional processing, or social exclusion (de Wit et al., 2022).
- 6 microdoses of LSD did not impact reaction time, paired associates learning, rapid visual information processing, spatial WM (Family et al., 2019).
- Psilocybin improved convergent and divergent thinking (Prochazkova et al., 2018).
  - Psilocybin retreat, not placebo-controlled, probably practice effects.
- Enhanced sustained attention and positive mood but also increased anxiety (Hutten et al., 2020).
  - Caffeine deprived

Temporal Reproduction

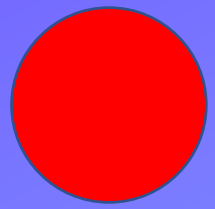
Yanakieva. (2019)



Wackerman et al. (2008)



Temporal Dilation?



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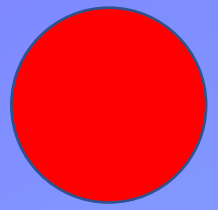

2 seconds

2 seconds

Why would observing a red dot on the screen feel longer under LSD but not yourself holding down a button?

El Greco Fallacy

- Assumption that particular perceptual abnormalities will influence interactions with the world of a similar nature.
- Firestone & Scholl (2013)
  - Holding a rod horizontally doesn't actually make a hallway look narrower.
  - Thinking darker thoughts doesn't actually make the world look darker.

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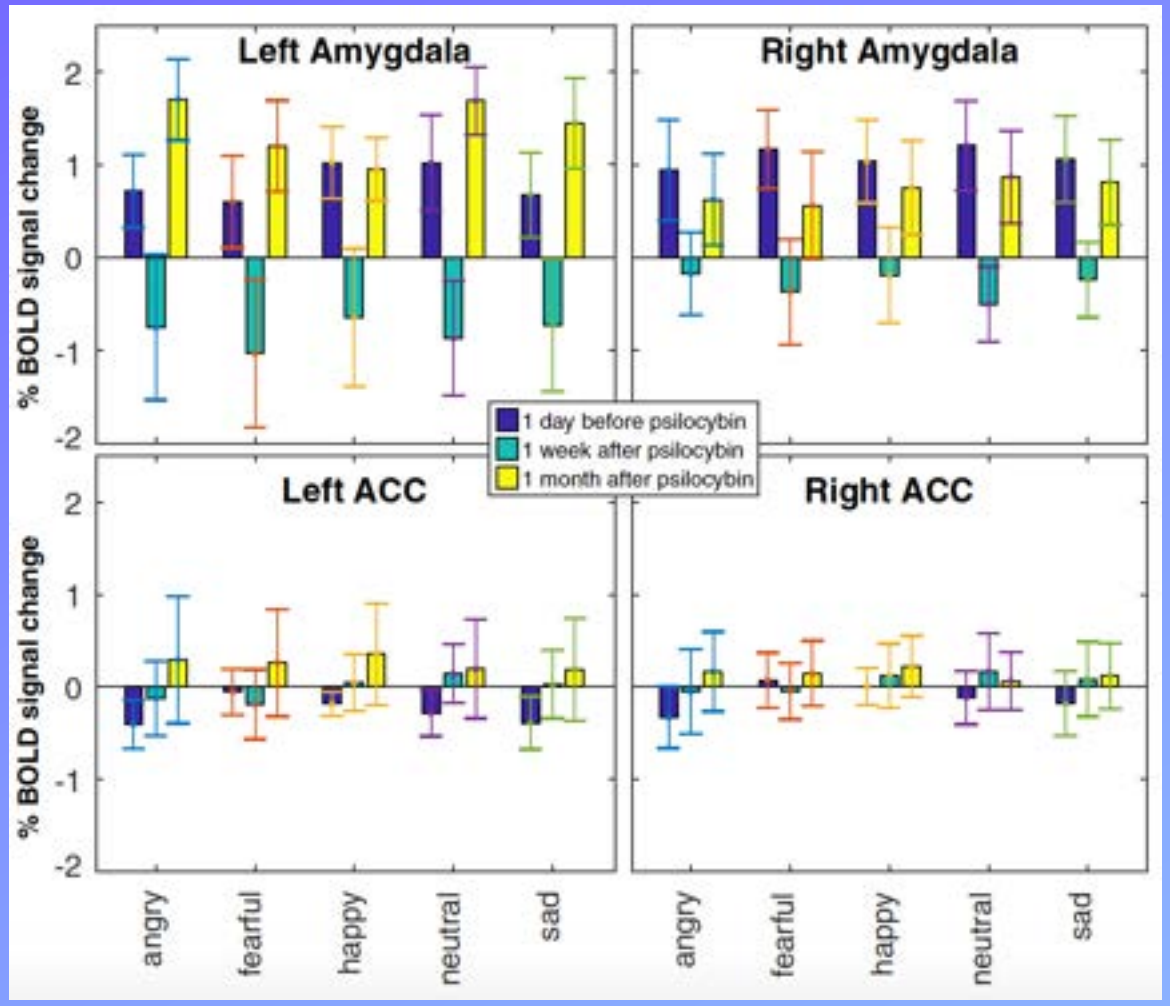
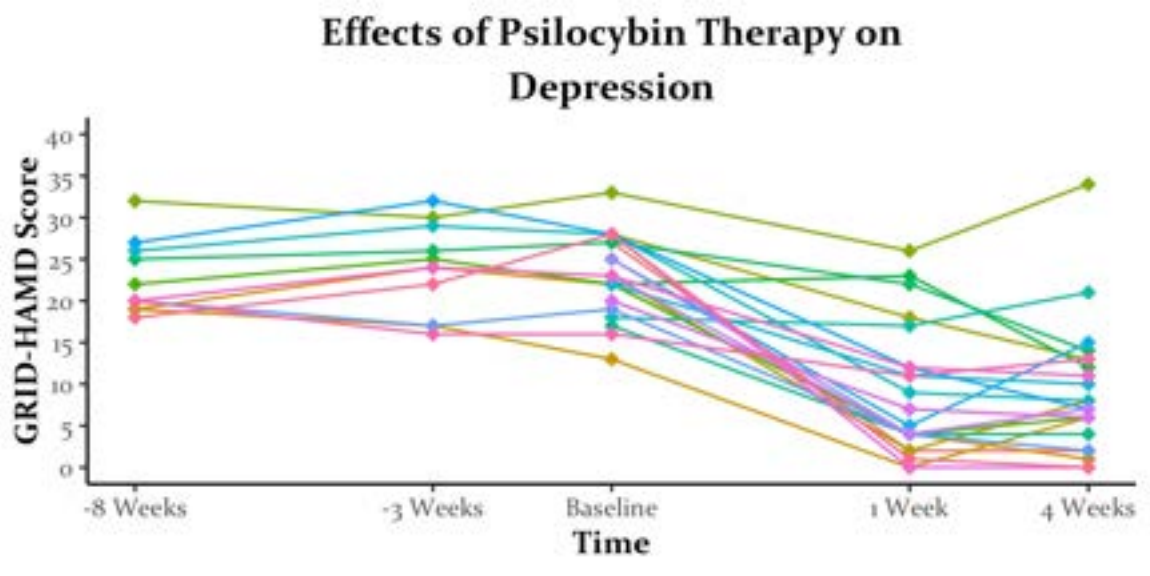
Psilocybin Blunt Amygdala Reactivity 1 Week After a Single High Dose

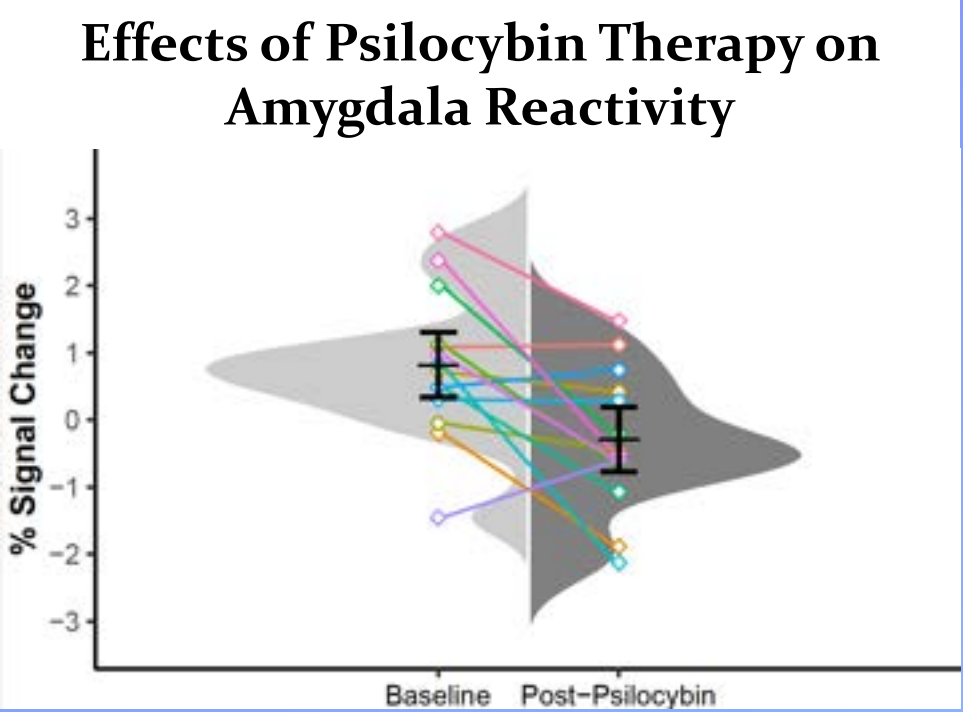


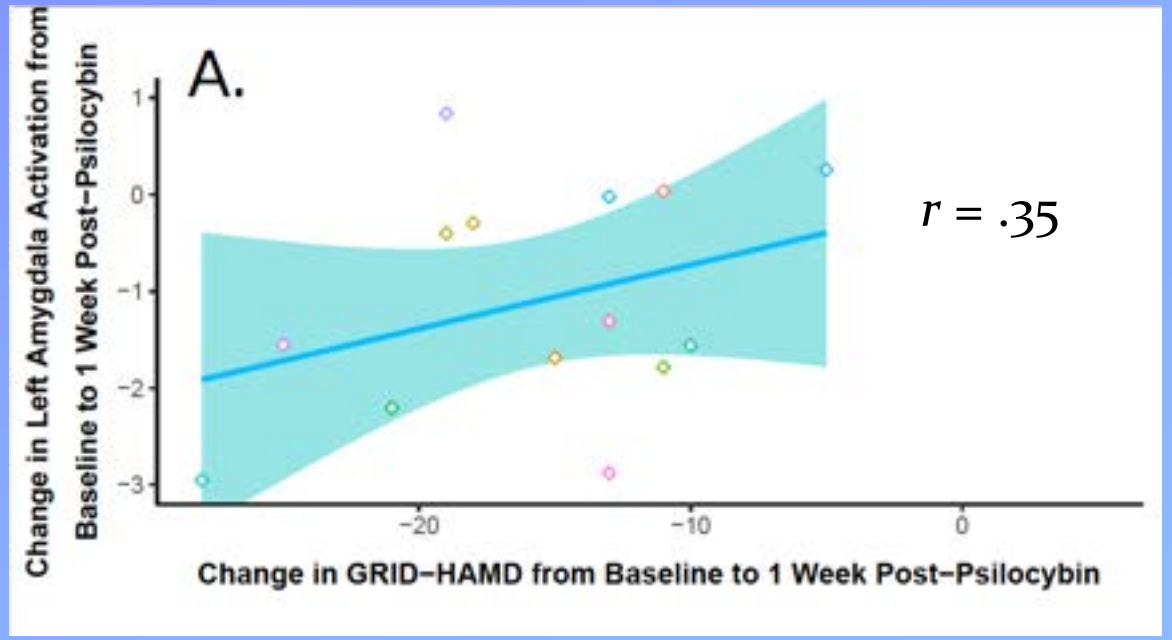
- Reductions in negative affect:
  - DASS stress
  - PANAS negative affect
  - STAI state, trait
  - POMS tension, depression, mood disturbance
- Increases in positive affect:
  - DPES content, pride, compassion, amusement

Barrett, Doss, et al. (2020), *Scientific Reports*

Also in patients with depression…







Barrett, Doss et al. (in review)

Background for Depression Study

- Psychedelic therapy is showing potential for the treatment of depression and other psychiatric disorders[1].
- Depression and other disorders are accompanied by cognitive rigidity[2] and less neural dynamics[3].
  - Cognitive flexibility - Ability to adaptively switch between different cognitive operations in response to changing environmental demands.
  - Neural flexibility - Variability/complexity of brain signals over time.
- A potential transdiagnostic mechanism of psychedelic therapy may be enduring enhancements of cognitive & neural flexibility.

[1]Carhart-Harris et al. (2016, 2021); Davis et al. (2020), Johnson et al., (2014), Moreno et al. (2006)
[2]Gruner et al. (2017), Strange et al. (2017), Verdejo-Garcia et al. (2015)
[3]Goodman et al. (2021), Zheng et al. (2018)

Psychedelics and Cognitive & Neural Flexibility

- Cognitive flexibility supported by neural flexibility, especially of anterior cingulate cortex[1] (**ACC**).
  - Neural flexibility ≠ cognitive flexibility
- Psychedelics acutely acutely increase some measures of (task-free) neural flexibility (e.g., entropy), especially of ACC[2] but acutely impair cognitive flexibility[3].
- In healthy populations, mixed evidence regarding subacute (1 day) effects of psychedelics on cognitive flexibility[4] and no apparent enduring (1 week) effects on neural flexibility[5].
- What are the enduring effects of psychedelics on cognitive & neural flexibility in patients with major depressive disorder (MDD)?

[1]Chen et al. (2016), Fu et al. (2022)
[2]Tagliazucchi et al. (2014), Lebedev et al. (2016)
[3]Amodeo et al. (2020), Pokorny et al. (2019)
[4]Murphy-Beiner et al. (2020), Wießner et al. (2022)
[5]Barret et al. (2020)

Study Design

- Open-label clinical trial testing psilocybin therapy for MDD
- ≤24 patients with MDD (8 males) and limited hallucinogen use
- 20 and 30 mg/70 kg psilocybin sessions separated by ≈1.6 weeks
- Immediate group and 8-week delayed control group
- Cognitive testing and 7T neuroimaging (fMRI and MRS) assessed at baseline and 1 week after psilocybin therapy (cognitive testing also 4 weeks post-treatment)
  - Cognitive measures assessed twice pre-treatment in delayed group to control for practice effects.

Cognitive Flexibility

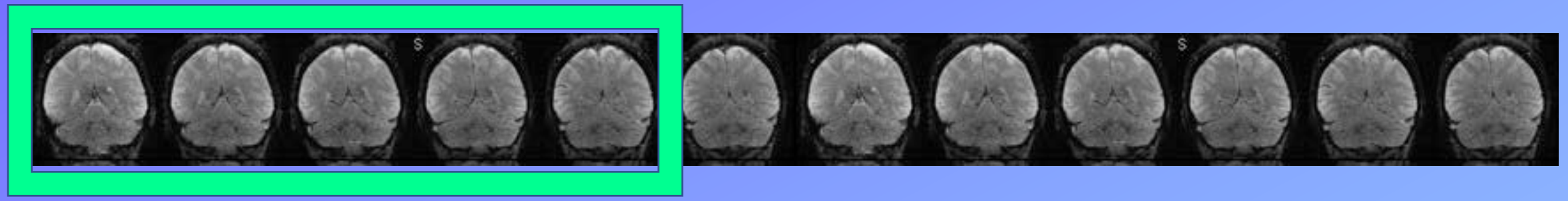
- Penn Conditional Exclusion Test (PCET)[1]

- Perseverative errors = 3 errors in a row based on prior rule
  - Less errors = **greater** cognitive flexibility
- Multiple versions to minimize learning effects.

[1]Kurtz et al. (2004)

Neural Flexibility

time

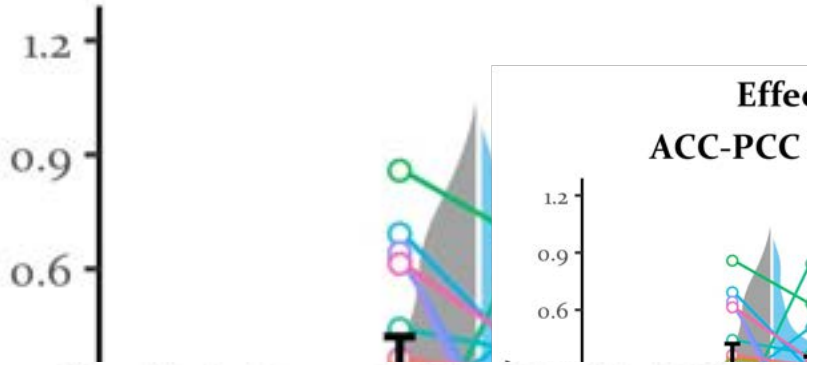


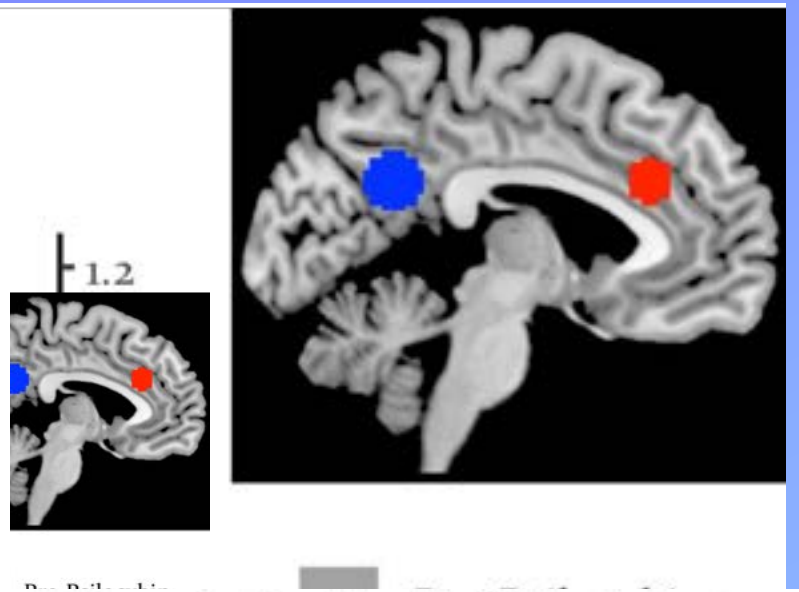
r_1 r_2 r_3 r_4 r_5 r_6 r_7 r_8

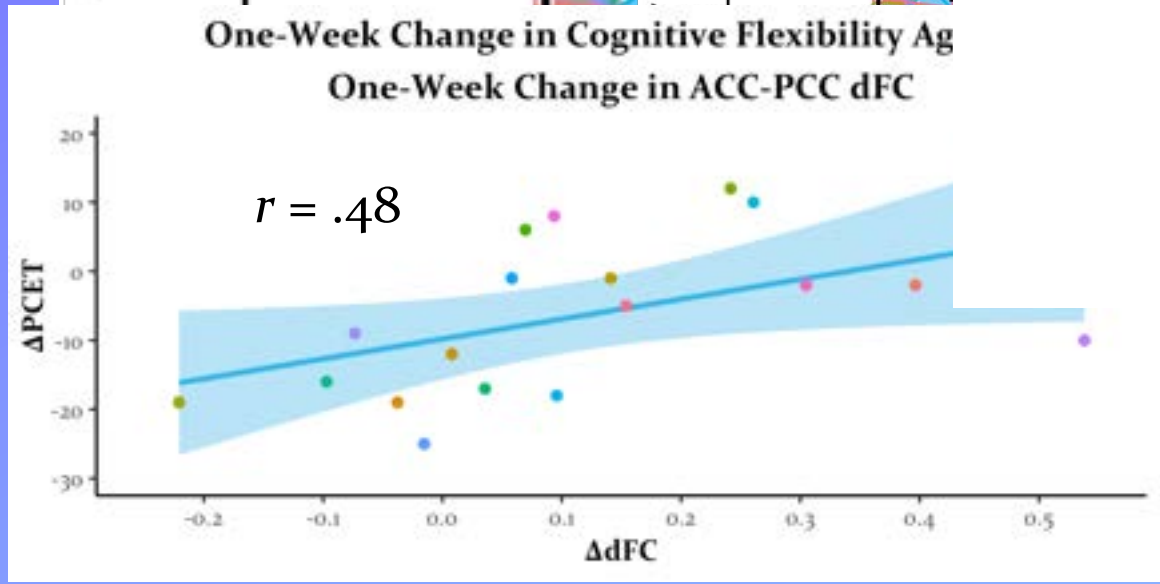
σ^2

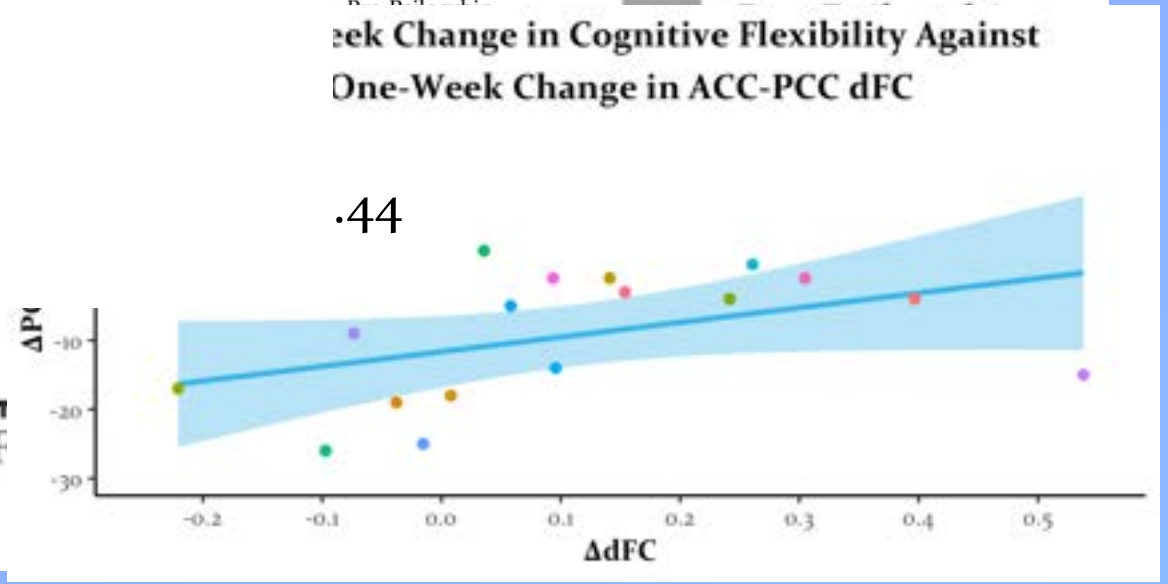
$\sigma^2(R)$ = dynamic functional connectivity (dFC)

Effects of Psilocybin on ACC-PCC Functional Connectivity

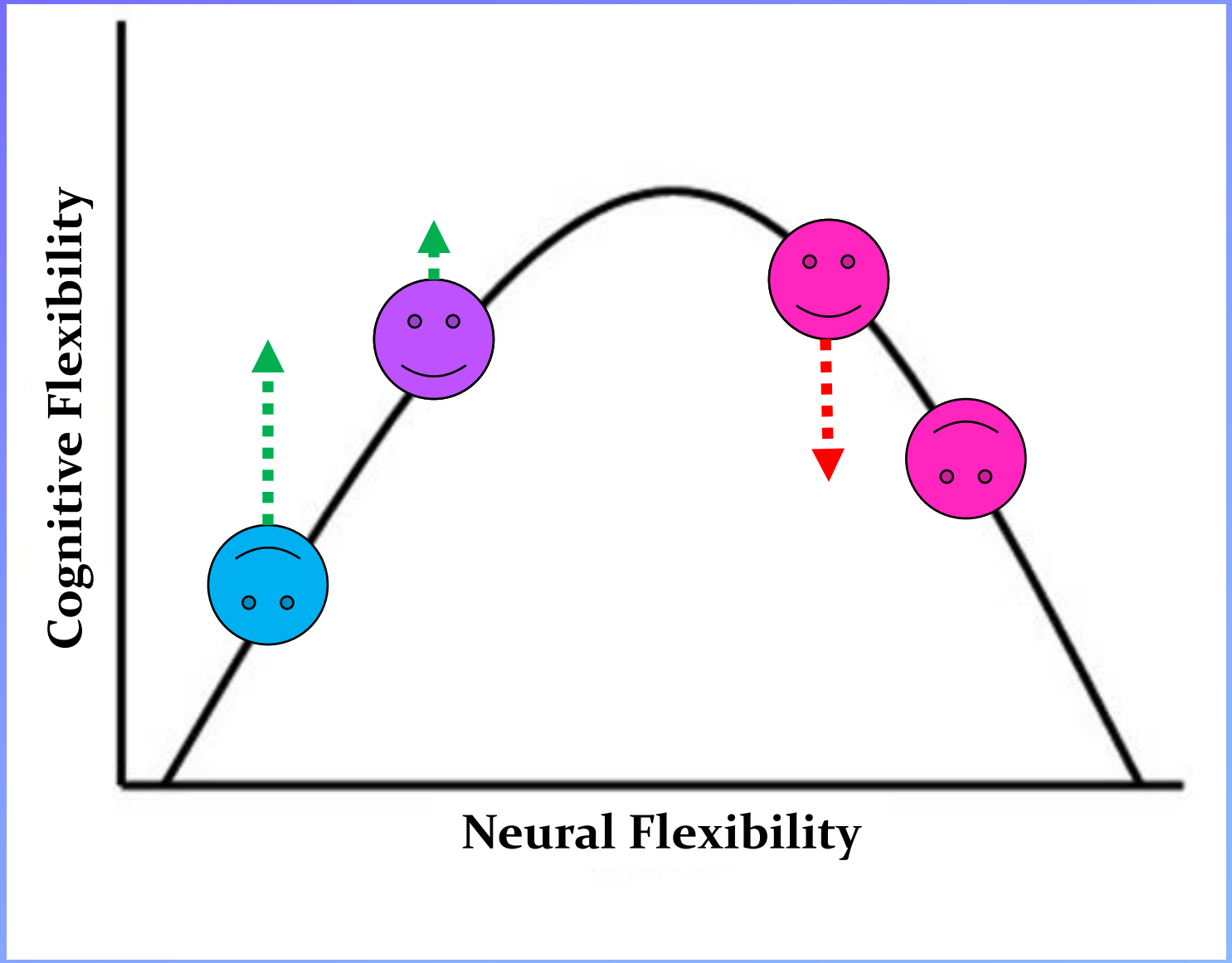








Doss et al. (2021), *Translational Psychiatry*


Cognitive Flexibility
Neural Flexibility

ARTICLES

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nature medicine

Increased global integration in the brain after psilocybin therapy for depression

Richard E. Daws[1,2,5], Christopher Timmermann[1,3], Bruna Giribaldi[3], James D. Sexton[3], Matthew B. Wall[4,5,6], David Erritzoe[3], Leor Roseman[3], David Nutt[3] and Robin Carhart-Harris[3,7]

Response to psilocybin correlates with network flexibility. The specific changes in network recruitment observed 1 d after psilocybin therapy in the open-label trial were not replicated at 3 weeks in this DB-RCT (Supplementary Information). However, the faster fMRI scanning protocol adopted in the DB-RCT generated twice as much temporal data per scanning session (Methods). This provided the rare opportunity to examine changes in the dynamic flexibility of brain networks following psilocybin therapy.

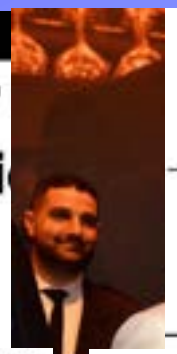
The metric known as 'dynamic flexibility' indexes how often brain regions change their community allegiance over time, during the course of an fMRI scan[33,34] (Methods). Reduced functional dynamics have been previously associated with depression symptomology[14]. In an exploratory analysis, post-psilocybin therapy

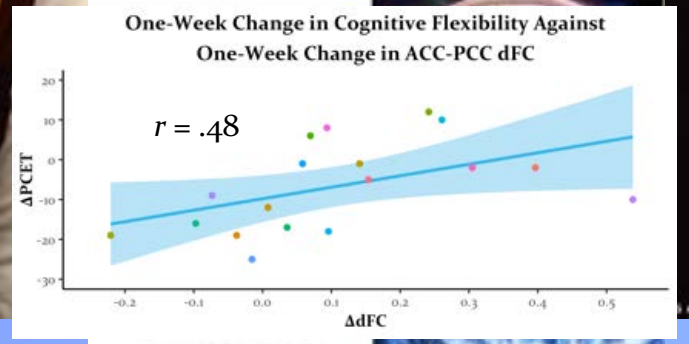
The EN and SN have been associated with tasks requiring cognitive flexibility such as learning and task switching[18,19,46,47]; impaired functioning of these networks have been reported in depression[14,17] and other disorders exhibiting cognitive inflexibility such as autism spectrum disorder[48] and obsessive–compulsive disorder[49]. Our results suggest that decreased modularity or increased flexibility of these networks following psilocybin therapy is a key component of its therapeutic mechanism of action. We did not formally assess cognitive flexibility in the clinical trials reported here but we did observe improvements in general cognitive functioning after psilocybin treatment in the DB-RCT, as well as treatment-specific improvements in 'emotional avoidance' (an inversion of the related construct 'psychological flexibility'[26]).

VICE

Inside the Dispute Over High-Profile Psychedeli Study

Decreased brain modularity for psilocybin but not escitalopram. Reconfirming our primary hypothesis (Fig. 5a,b) and replicating analyses on the open-label trial data, brain network modularity was significantly reduced at the trial's primary end point, 3 weeks after psilocybin therapy (mean difference, −0.39; $t_{21}=-2.20$, 95% CI −0.75 to −0.02, $P=0.039$, $d=0.47$). Moreover, for the psilocybin condition, post-treatment decreases in brain network modularity significantly correlated with improvements in depression symptom severity at this primary end point ($r_{20}=0.42$, $P=0.025$, one-tailed).





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Viewpoint

Skepticism about Recent Evidence That Psilocybin "Liberates" Depressed Minds

Manoj K. Doss,* Frederick S. Barrett, and Philip R. Corlett

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A critique of: Skepticism About Recent Evidence that Psilocybin Opens Depressed Minds

AUTHORS
Robin Carhart-Harris, Richard E Daws, David Nutt

Conclusions

- Psychedelics reliably reduce ***task-free*** functional connectivity in the DMN, but so do other drugs, and this effect doesn't seem to be the strongest effect on brain function.
- Full doses of psychedelics broadly impair cognition, but they might enhance selective cortical processes (e.g., familiarity, semantic priming, "pop-out effect").
- Jury is still out if microdosing is better than a cup of coffee and if the mood enhancements are sustained and safe.
- Psychedelics are promising for the treatment of depression and maybe other disorders but probably not for everybody.

Shout-Outs

Fred Barrett
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Darrick May
Matt Johnson
John Clifton
David Gallo
Harriet de Wit
Josh Koen
Jason Samaha
Michal Povazan
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