



**University of
Zurich^{UZH}**

Yale University

Circuit Mechanisms of Action of Classic Psychedelics and MDMA

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KHP is currently an employee of Boehringer Ingelheim GmbH & Co. KG
This position is not related to the content of this talk.

Psychoactive Substances

Psilocybin



preferential **5-HT_{2A}** and **5-HT_{1A}** agonist

DMT



preferential **5-HT_{2A}** agonist

LSD



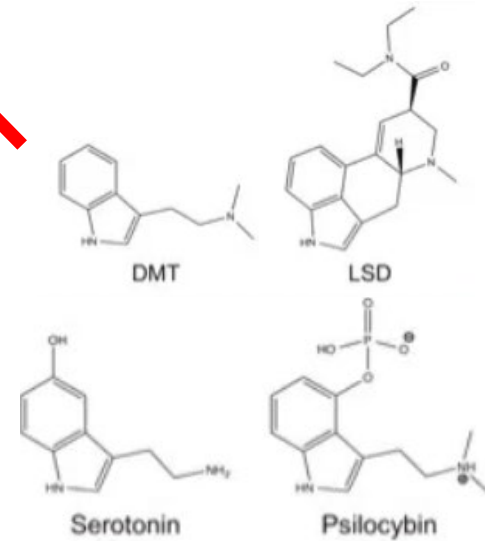
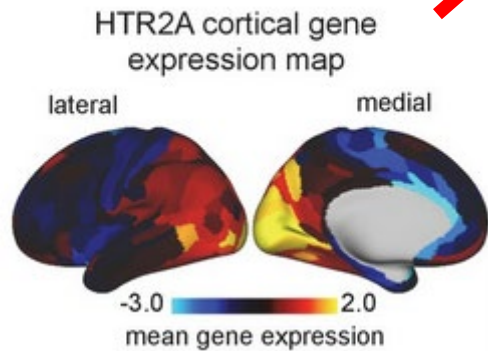
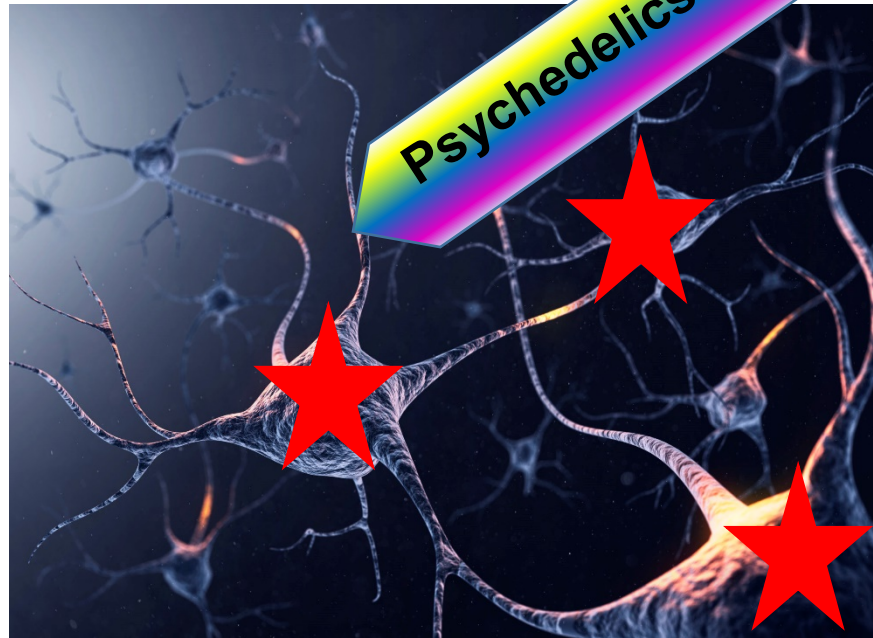
stimulates **serotonin** and **dopamine** receptors

MDMA

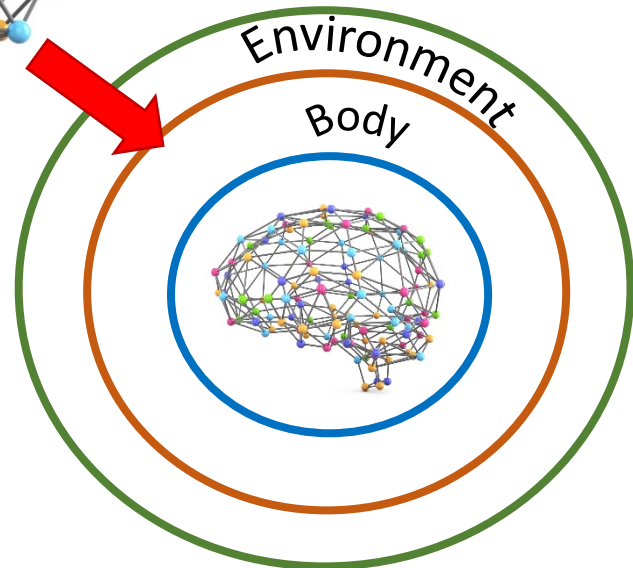
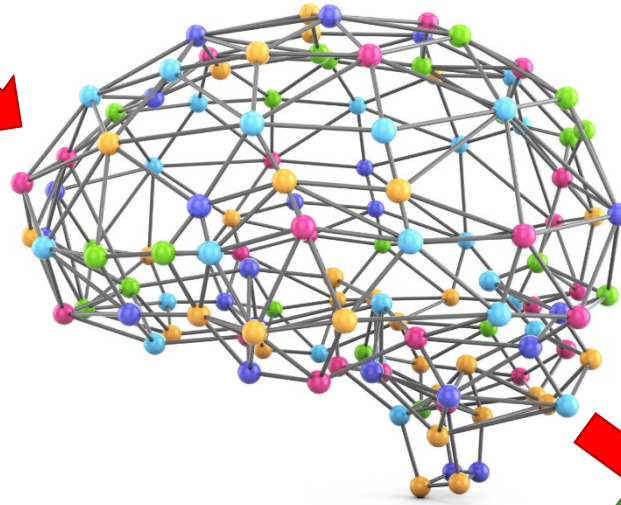
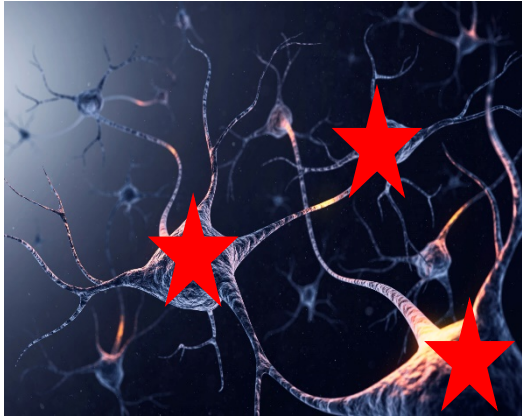


serotonin, **norepinephrine** and **dopamine** releaser

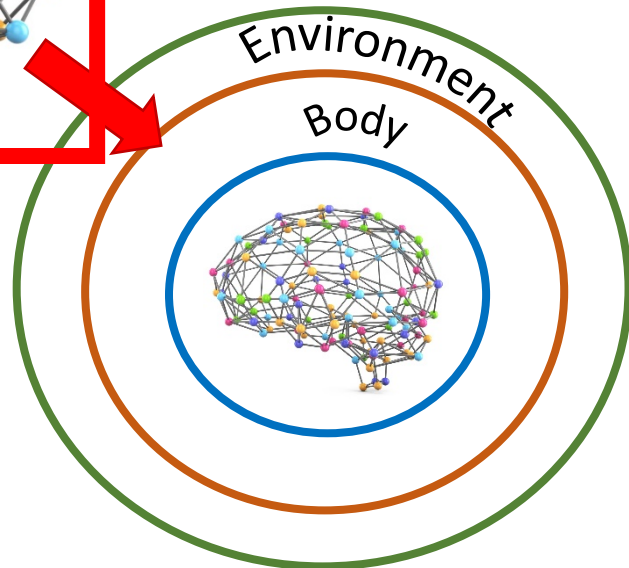
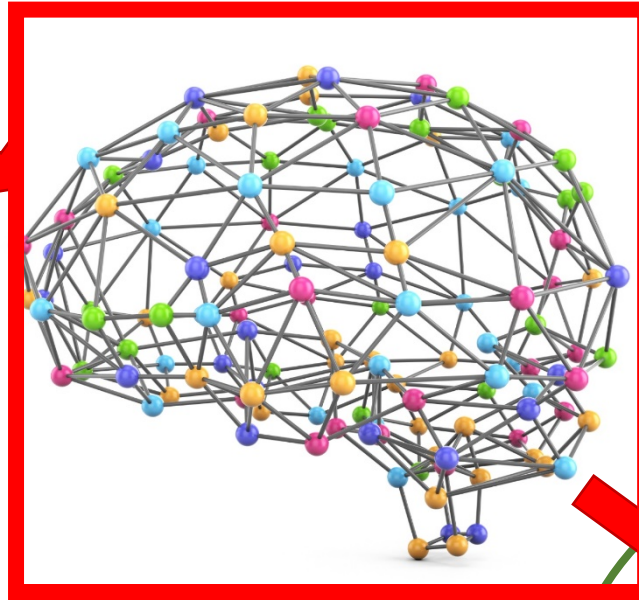
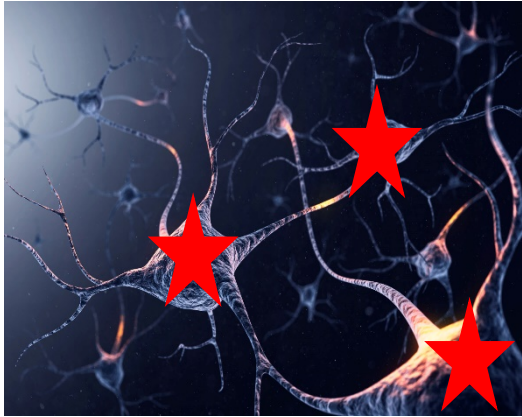
Psychedelics Change the Activity of Neurons



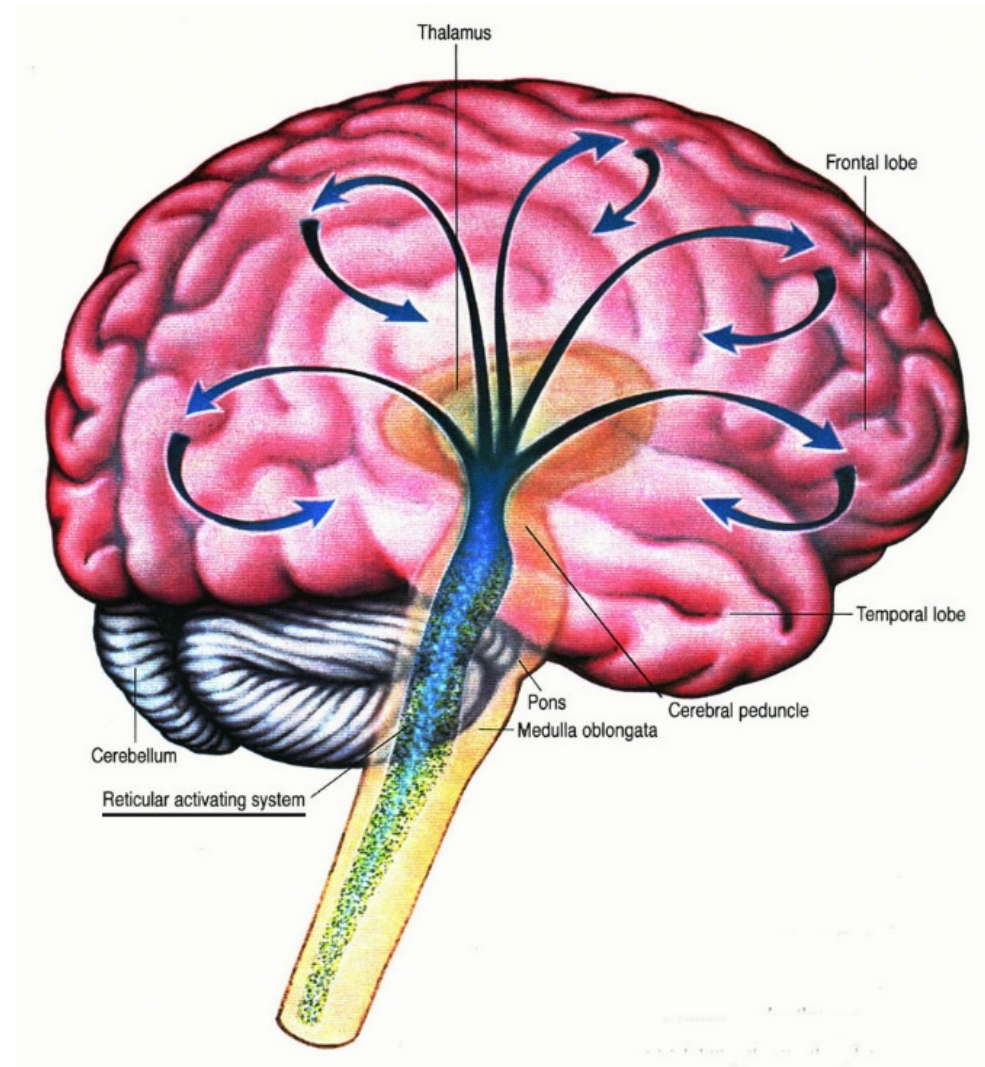
From Neurons to Interactions with the Environment



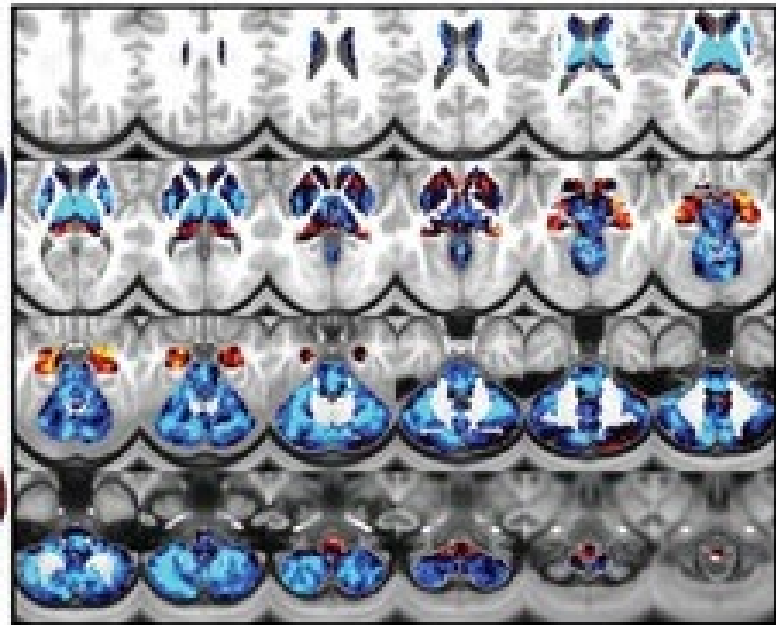
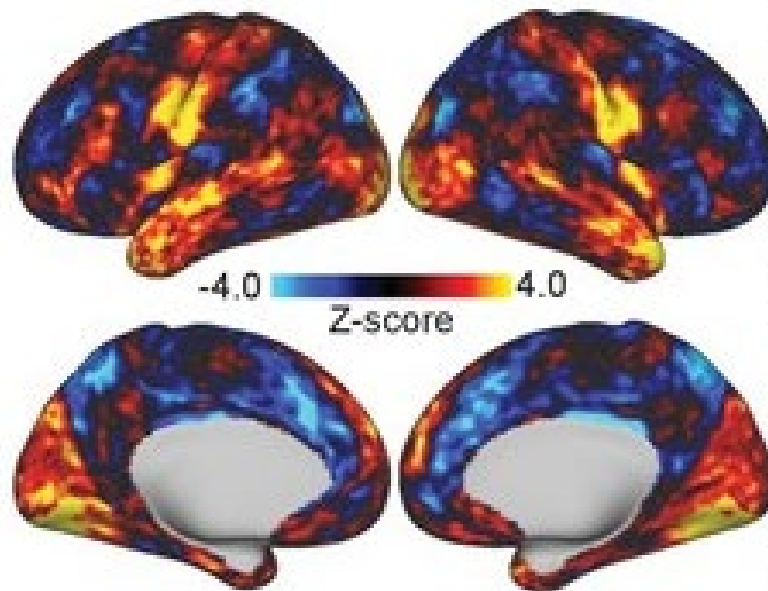
From Neurons to Interactions with the Environment



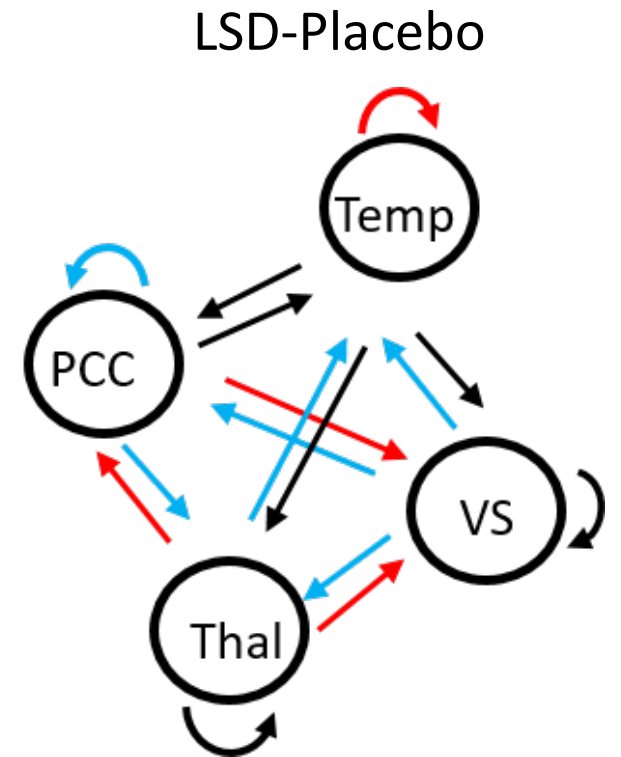
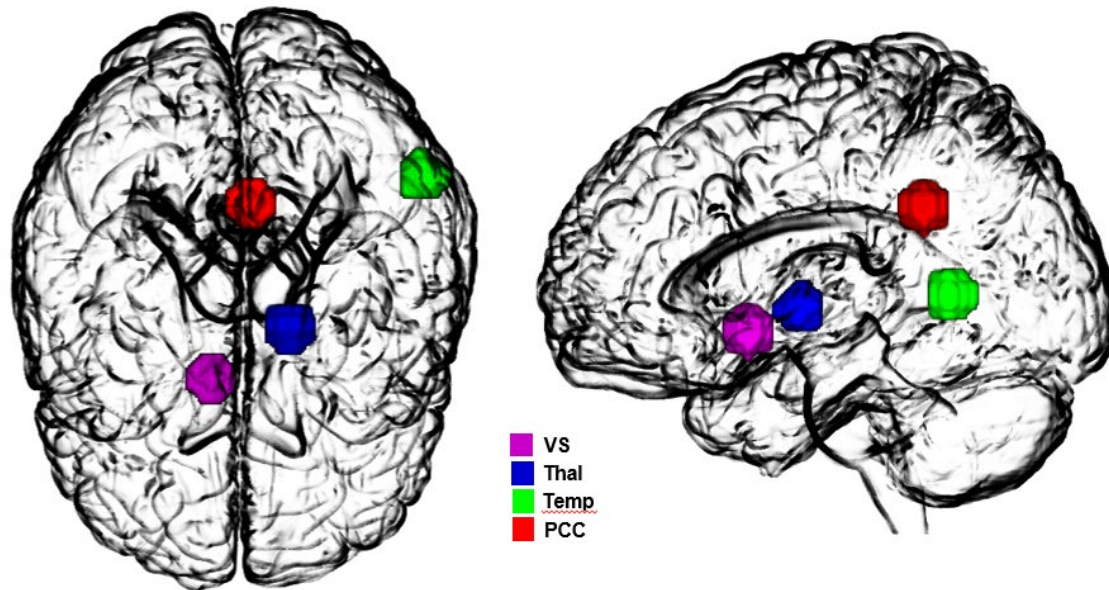
The Thalamic Filter Model



Thalamic Seed-Based Connectivity

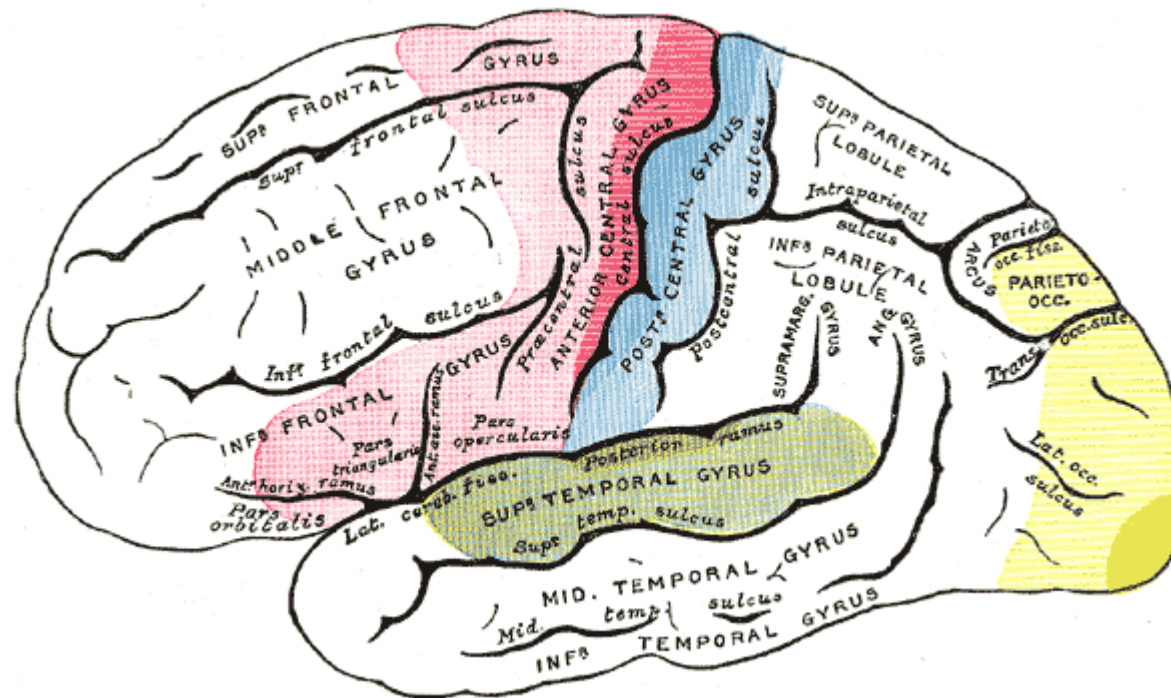


Thalamic Connectivity under LSD



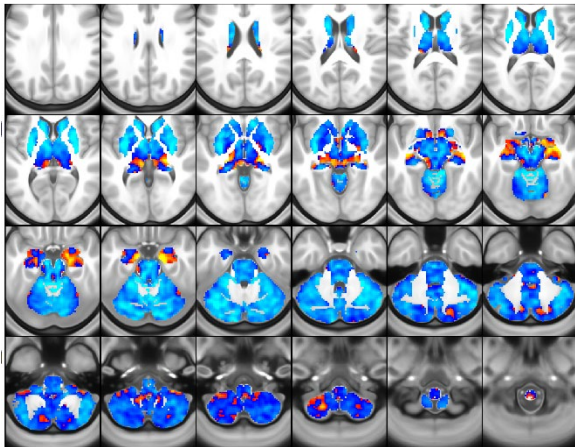
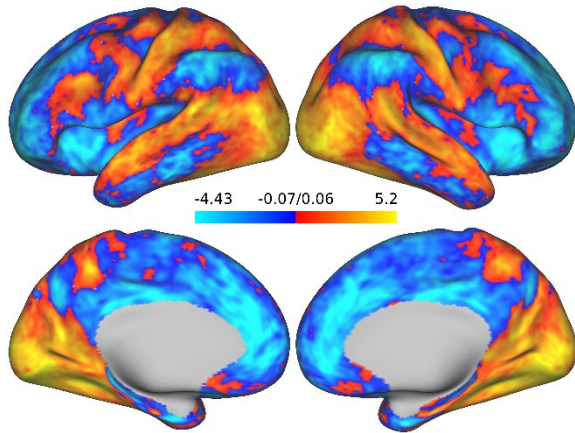
red: increased effective connectivity
blue: decreased effective connectivity

What about the Cortex?



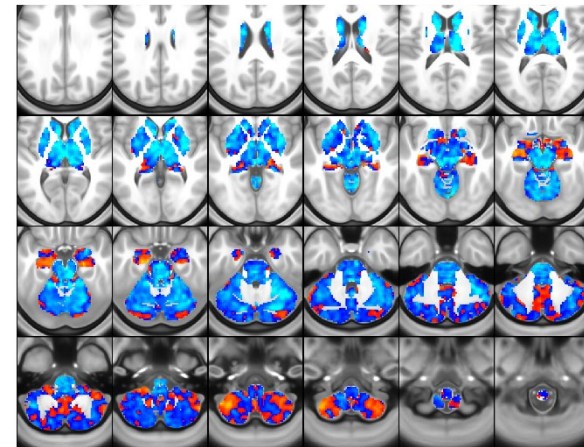
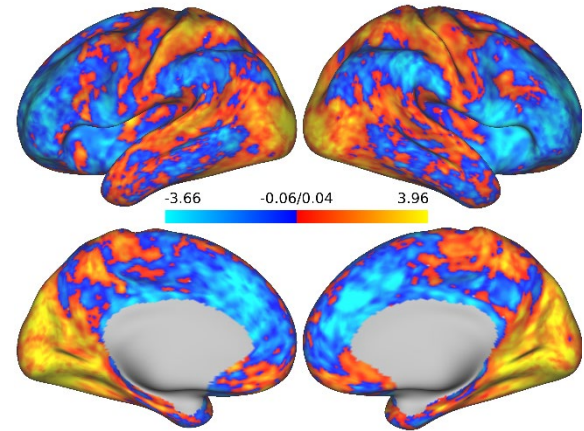
Changes in GBC are similar under LSD and Psilocybin

LSD vs. Placebo

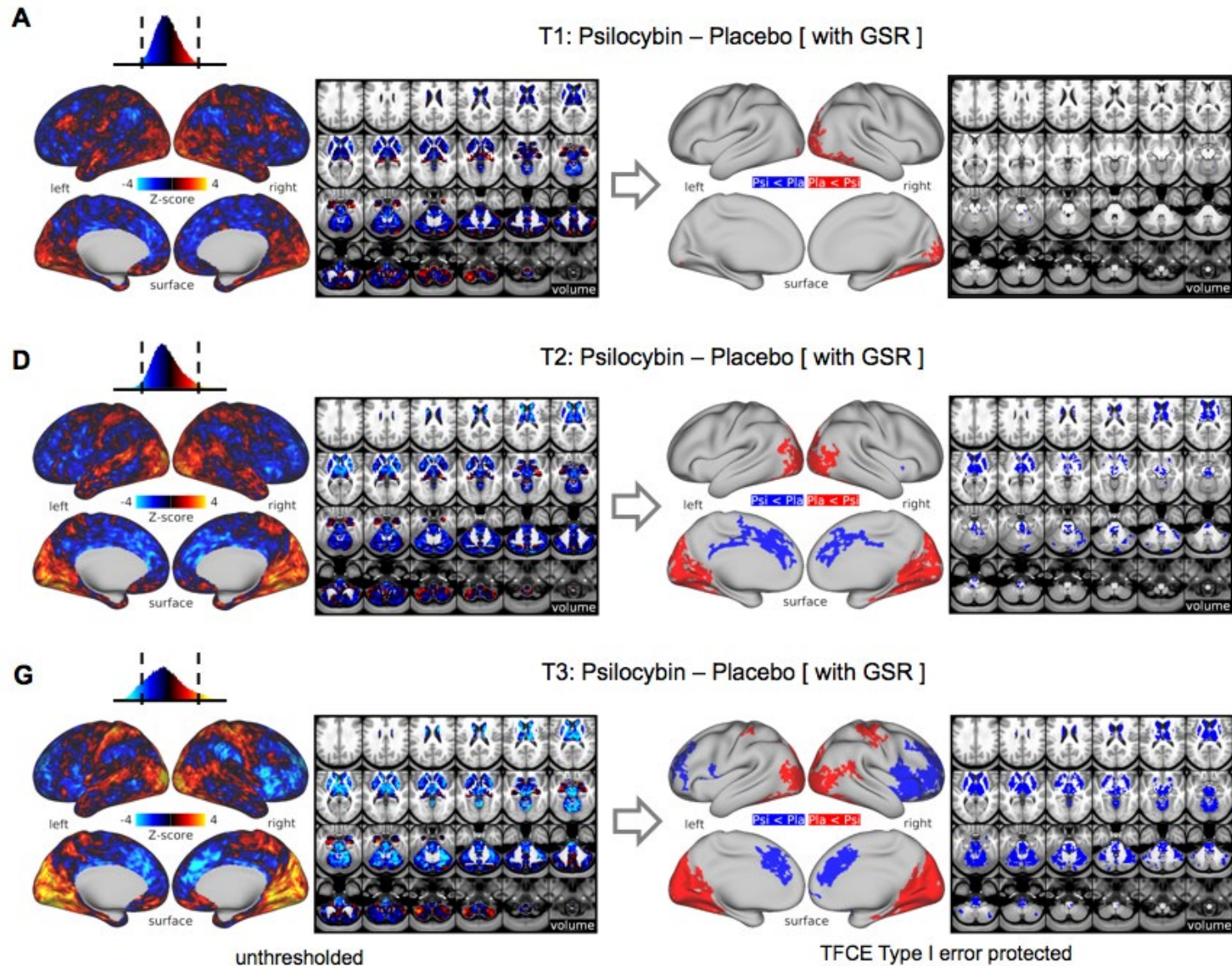


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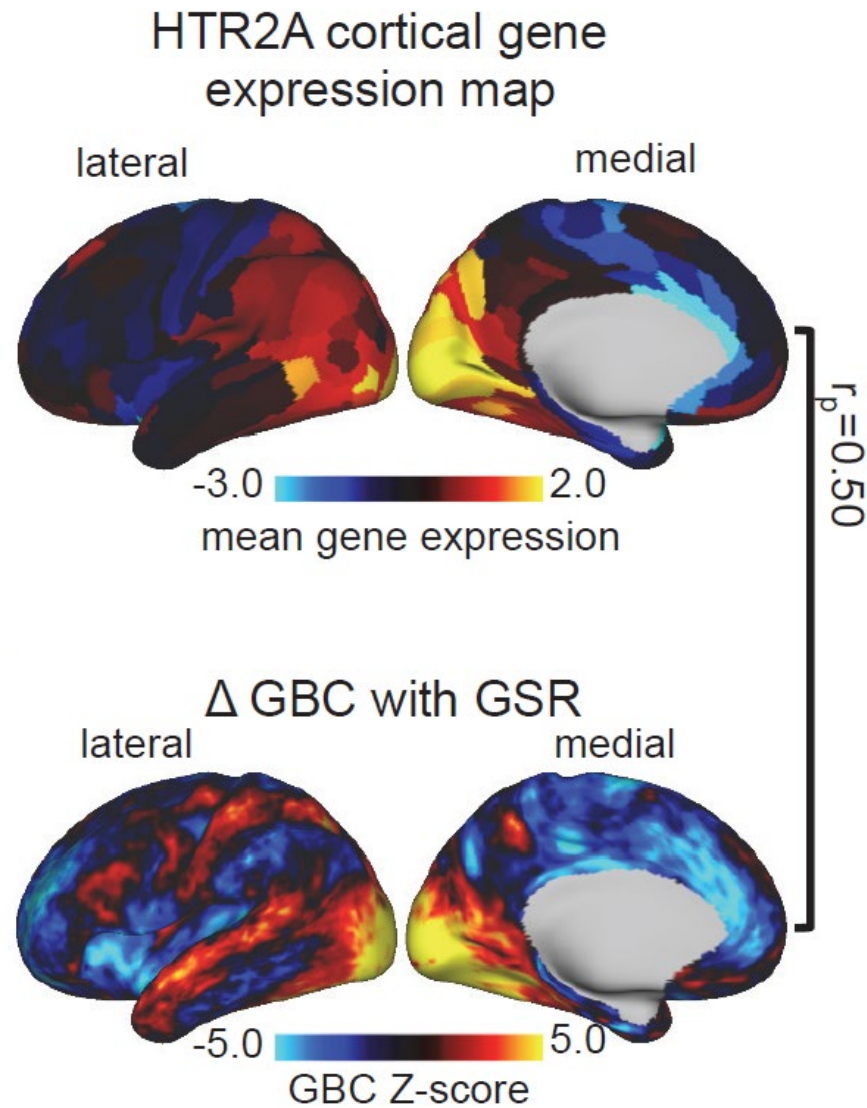
Psilocybin vs. Placebo



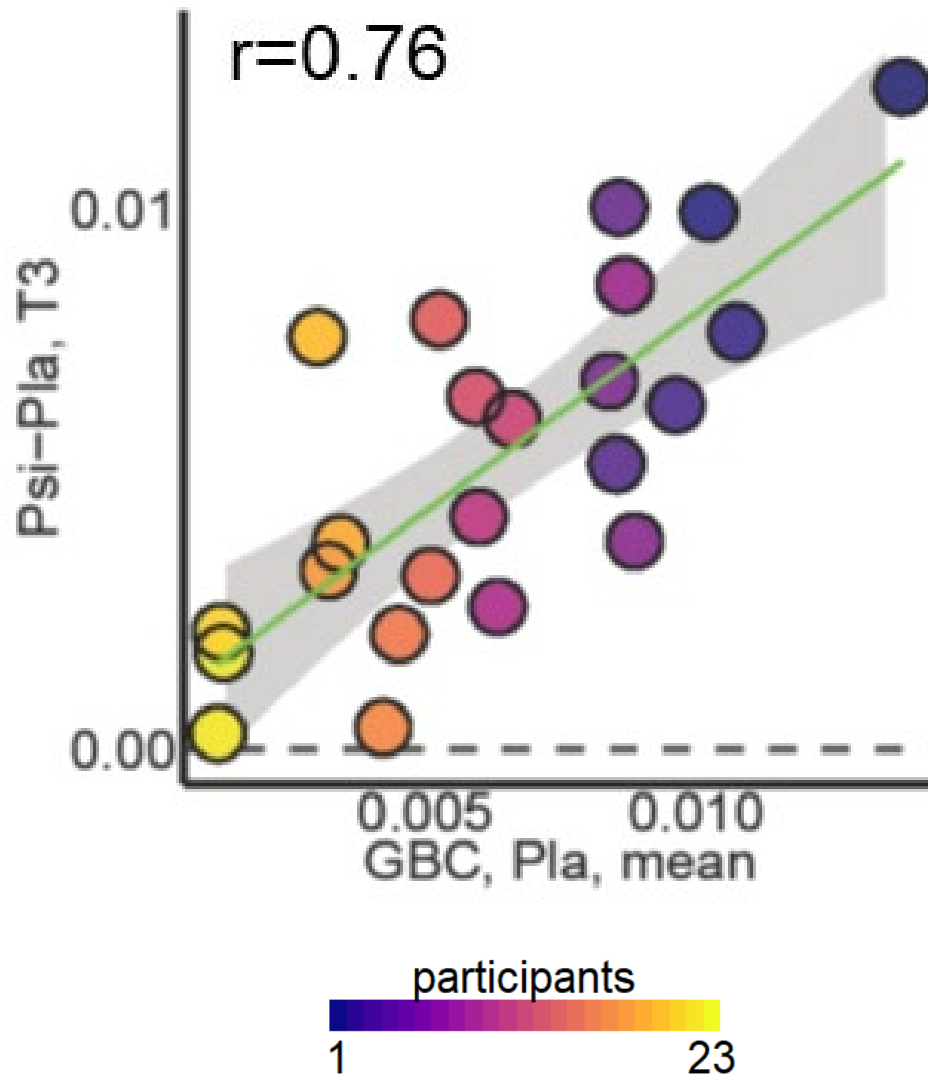
Time-dependent Effects of Psilocybin



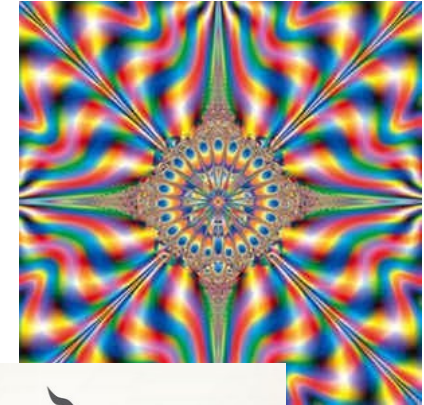
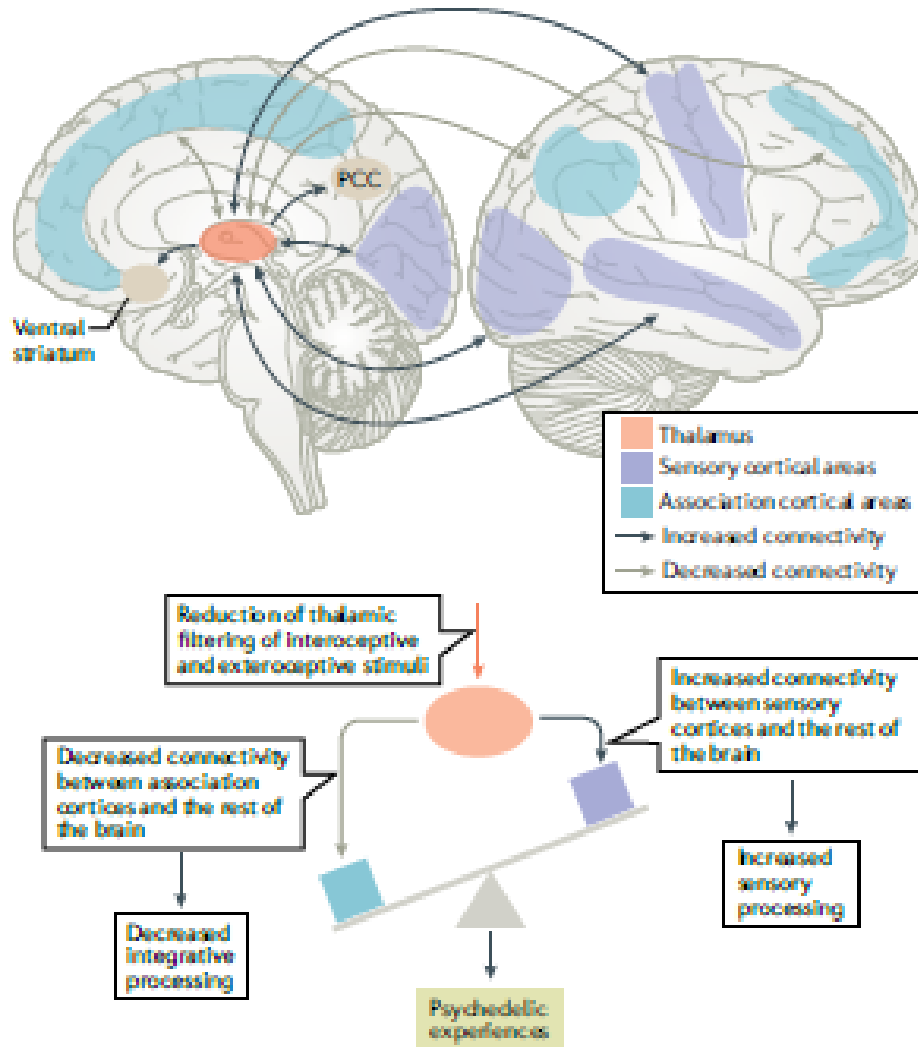
LSD-included Changes correlate with HTR2A Gene Expression



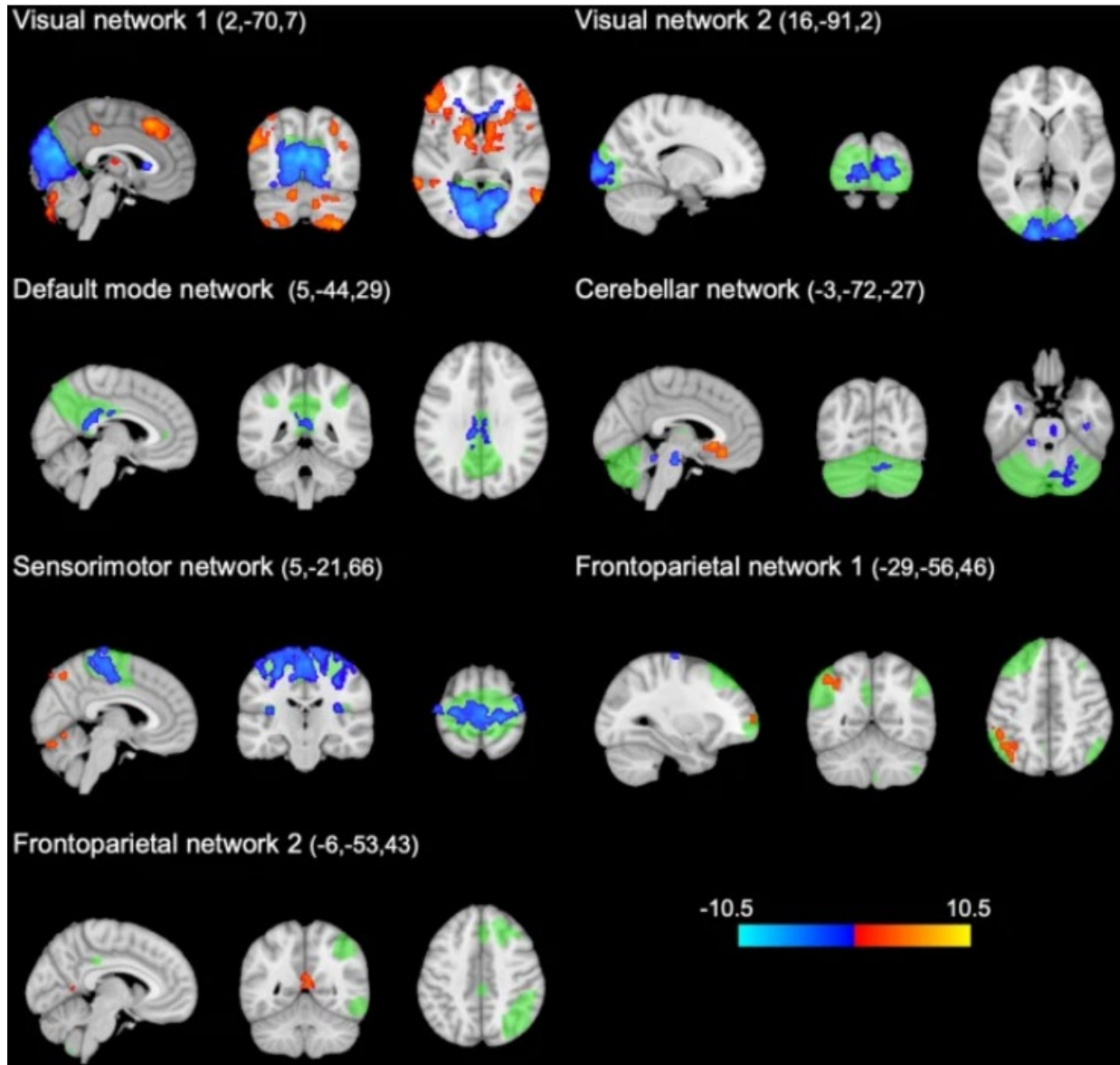
Baseline Connectivity Correlates with Magnitude of Psilocybin Effects



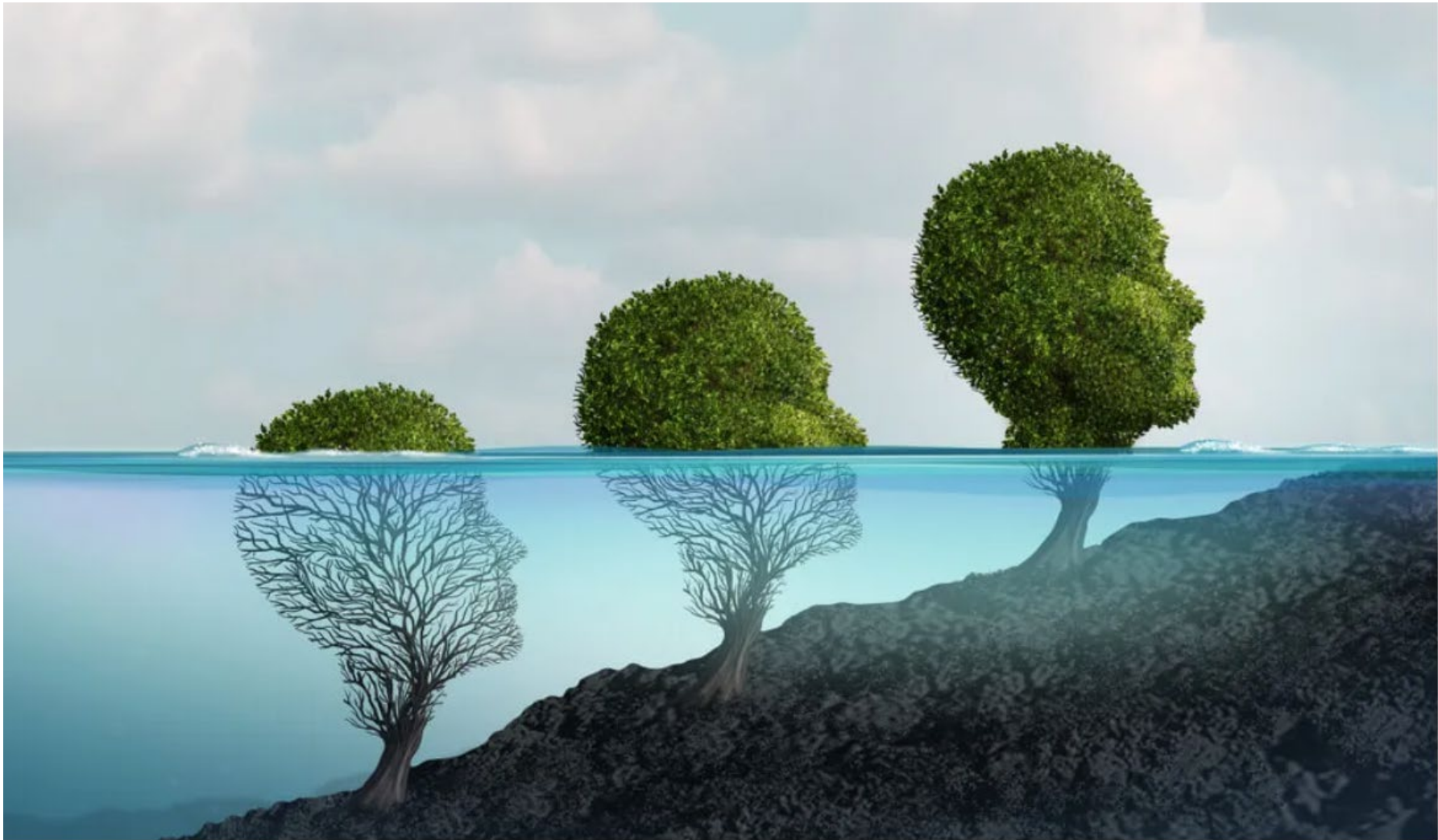
Dysbalance between Sensory Processing and Integration



Circuit-Level Changes under MDMA

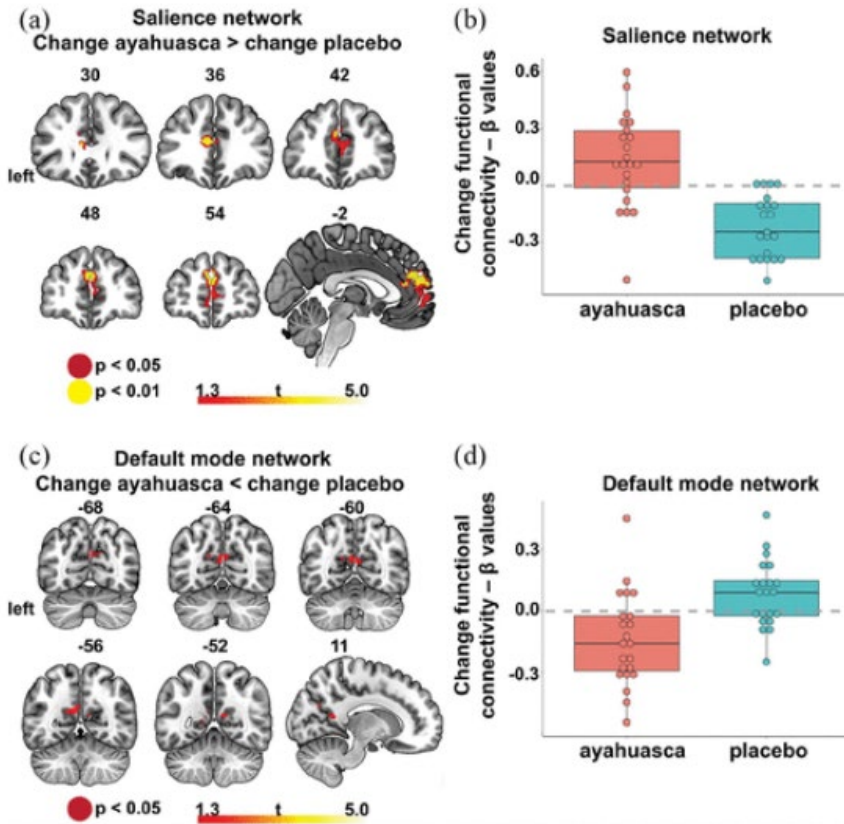


Lasting effects of single doses

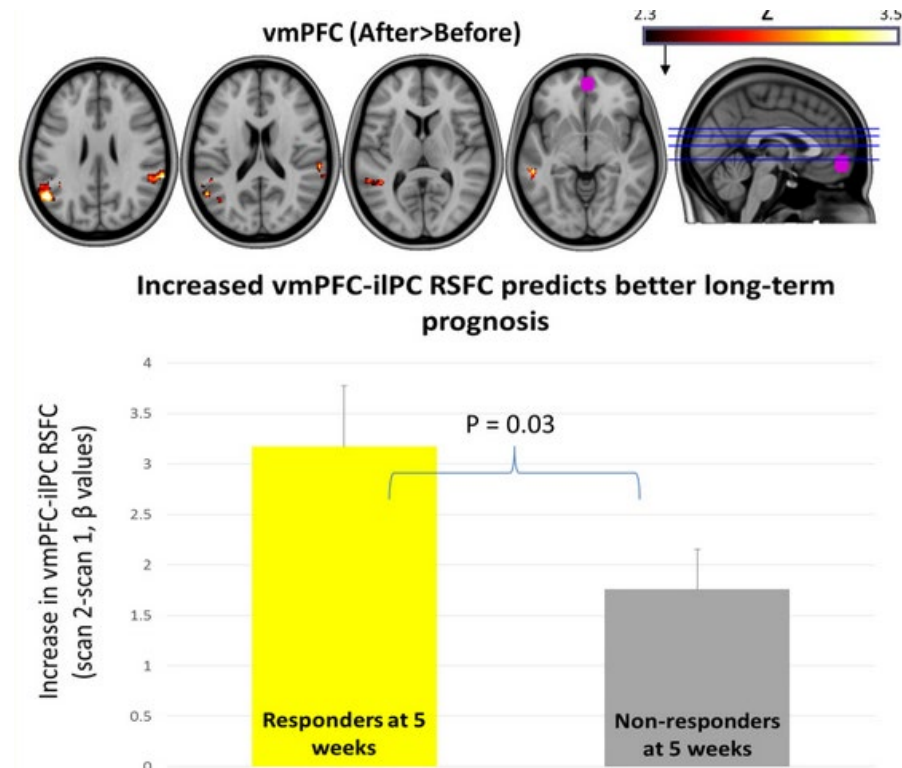


Post-acute Circuit Changes (24h)

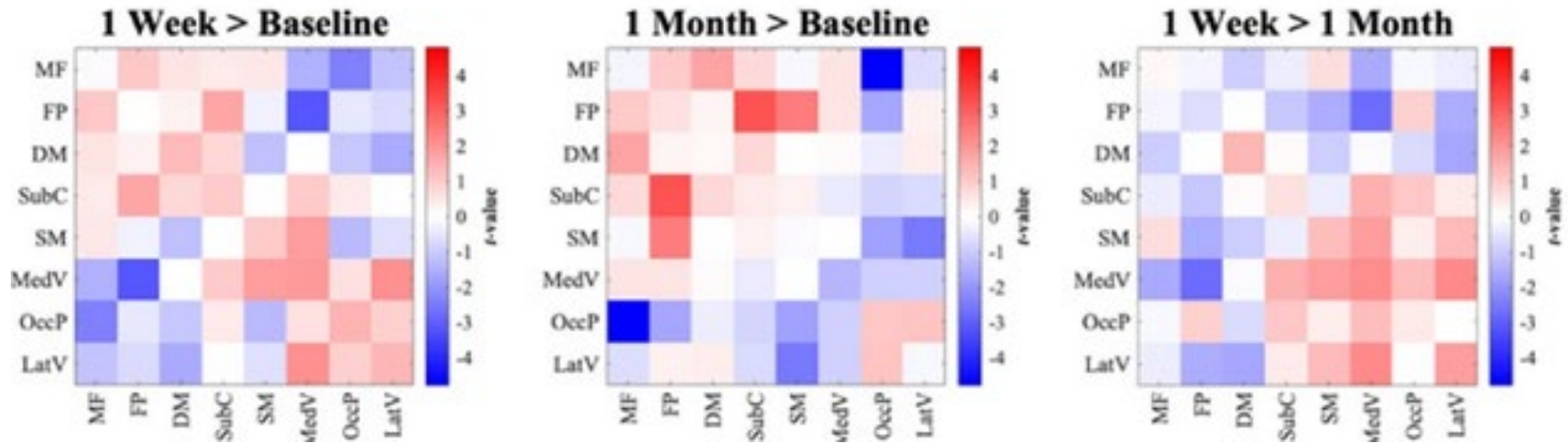
Ayahuasca: healthy participants



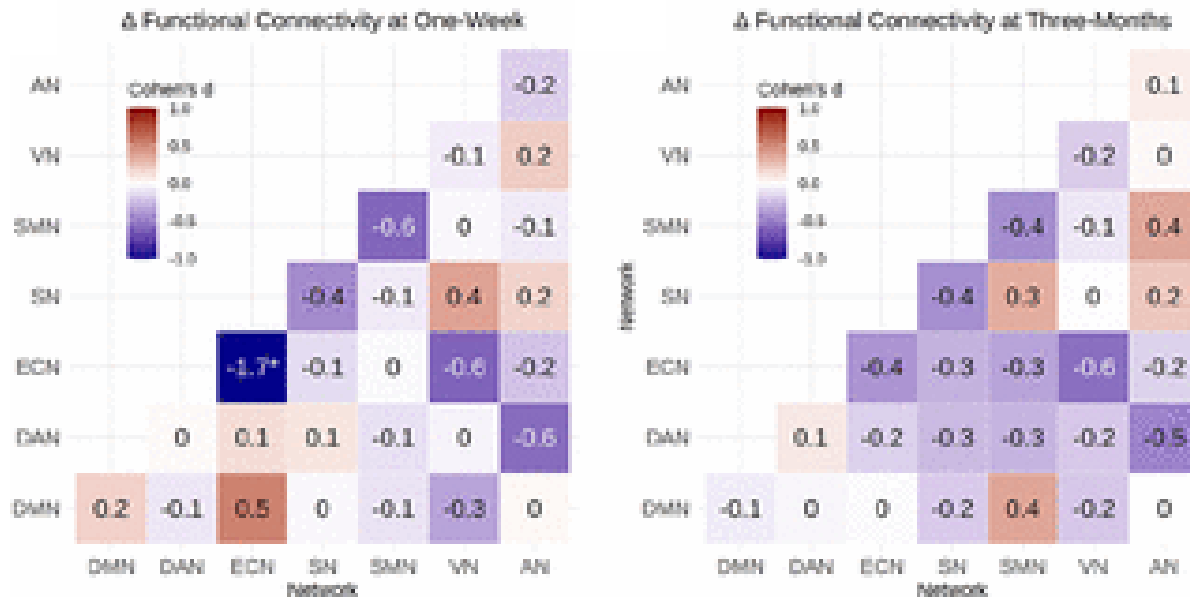
Psilocybin: depressed patients



Long-term Circuit Changes: No consistent pattern



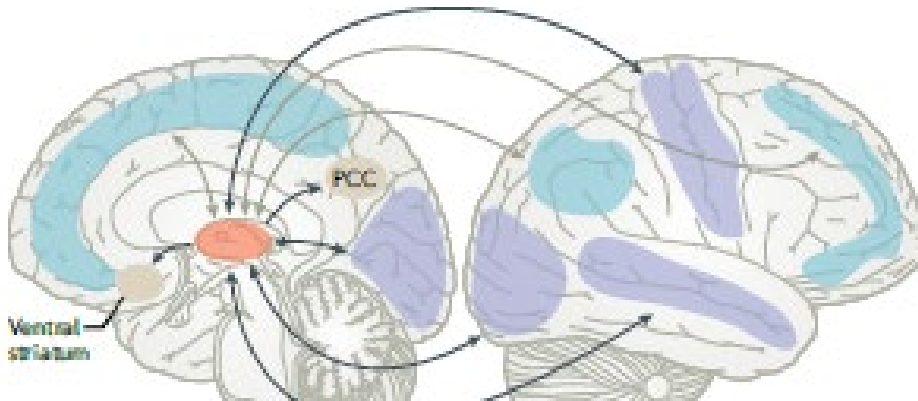
Barrett et al., 2020



McCulloch et al., 2022

Conclusions

- Acute changes in thalamic gating and network (dis-) integration
- Changes in functional connectivity align with 5-HT_{2A} receptor distribution
- Similar effects across psychedelics, not MDMA
- Inconsistent results on long-term changes so far



Knowledge Gaps

- How do circuit-level changes contribute to clinical efficacy?
- Trans-diagnostic mechanism is unclear
- Inter-individual variability is unclear
- Dose-response studies are missing
- Cross-pharmacology comparisons are needed to understand specificity of (network) effects

► **Understanding the mechanism of action is essential for optimizing the therapeutic approach**



Thank you!

Psychiatrische Universitätsklinik Zürich:

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