Awake Animal MRI: The Drug-Naïve Rat Brain on Psychedelics

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Introduction

Psychedelics are back in the clinic, but most of what is known about their whole-brain action comes from humans or from anesthetized animals, where anesthesia itself reshapes the BOLD signal.

We imaged fully awake, drug-naïve rats during a single intraperitoneal dose of six compounds, each in its own vehicle-controlled dose-response study, on one scanner with one protocol.

Is there a shared psychedelic signature in the naïve brain, or do these drugs differ in the sign, location and timing of their BOLD response?

6 compounds

244 awake rats

174 brain areas

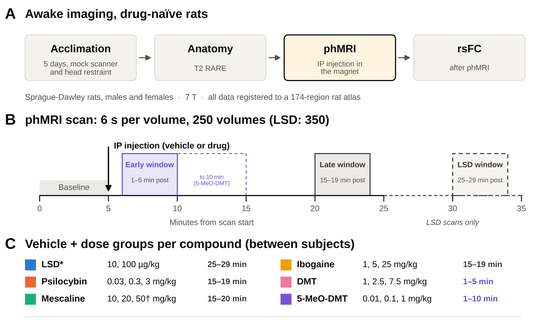
Methods

Awake imaging at 7 T after 5 days of acclimation to head restraint; T2 anatomy, 25-min phMRI with injection at 5 min, then a resting-state scan.

Data registered to a 174-area rat atlas; per rat and area, the volume with a significant positive or negative BOLD change from baseline.

Analysis window set by kinetics: 1–5 min for DMT (1–10 min for 5-MeO-DMT), 15–20 min for the others; LSD 25–29 min (prior study).

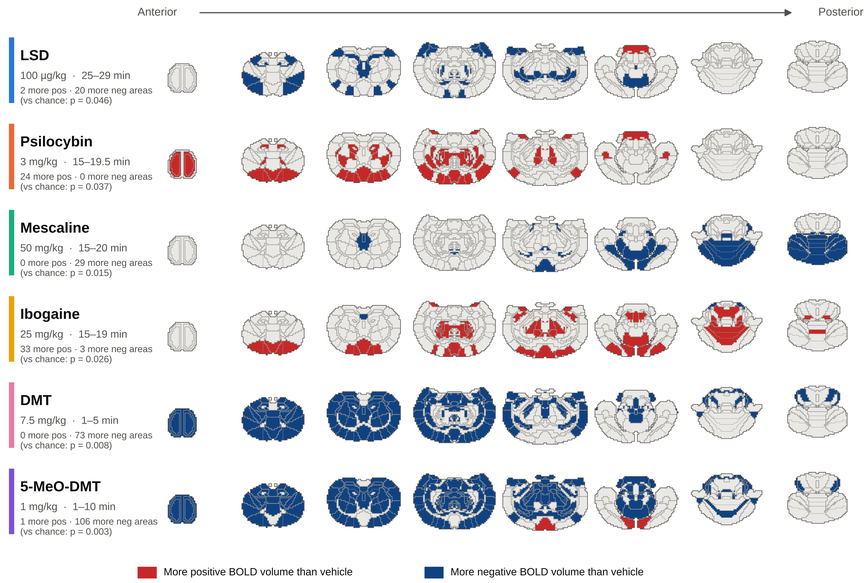
Rats are the statistical unit. Per area: highest dose vs vehicle, Mann–Whitney, $p < 0.05$, with a permutation check of the whole-brain count. Time courses: drug minus vehicle, no test.



References

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Cavallaro N, et al. Ibogaine dose-response in awake rats (under review).

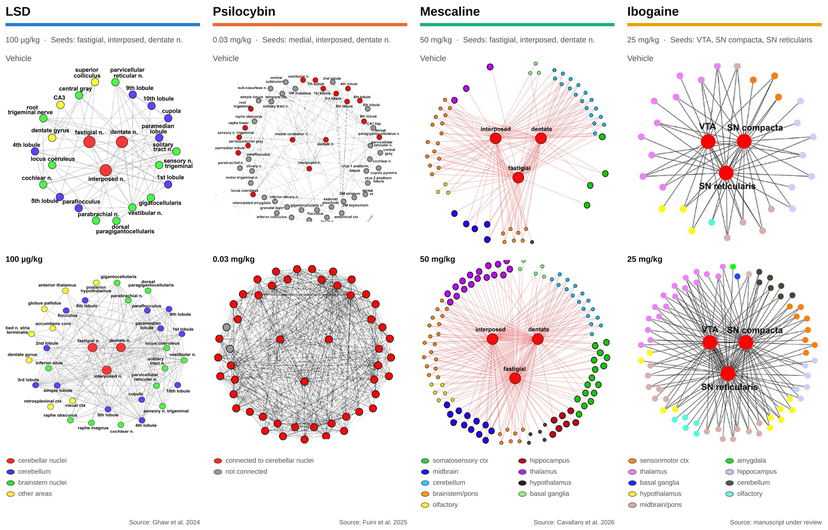
Highest dose vs vehicle: areas with more activated volume



Per brain area, rats as samples: highest dose vs vehicle, Mann–Whitney U (Kruskal–Wallis, two groups), $p < 0.05$, as in Ghaw et al. (2024) and the 5-MeO-DMT paper. About 4 areas per direction are expected by chance; chance p from 1,000 shuffles of group labels across rats. Psilocybin uses the published dataset (n = 33). Mescaline 50 mg/kg vs its 2024 vehicle; LSD 25–29 min. Doses are not equipotent.

Psilocybin and ibogaine are the only compounds that add positive BOLD volume relative to vehicle (24 and 33 areas): psilocybin in somatosensory cortex, ibogaine in thalamus, cerebellum and brainstem. The other four add negative BOLD volume: 20 areas for LSD, concentrated in olfactory and prefrontal cortex; 29 for mescaline, almost all cerebellar; 73 for DMT and 106 for 5-MeO-DMT, covering most of the forebrain within minutes of injection. Every count exceeds the ~4 areas expected by chance (permutation p = 0.003 to 0.046). The maps show increases only, so ibogaine's suppression of VTA and substantia nigra, which appears in these data as a loss of positive BOLD, is not colored here. No two compounds share a map.

Resting-state connectivity: seeded networks



In all four studies the drug network has more nodes and edges than vehicle. Seeded in the cerebellar nuclei, LSD at 100 µg/kg and mescaline at 50 mg/kg recruit cerebellar lobules and brainstem nuclei, and mescaline also thalamus, somatosensory cortex and hippocampus. Psilocybin at 0.03 mg/kg, the lowest dose tested, already links the cerebellar nuclei to nearly every node shown. Seeded in VTA and substantia nigra, ibogaine at 25 mg/kg adds thalamic, hippocampal, cortical and cerebellar partners. Thresholds and node sets follow each source analysis, so compare within a column, not across.

Time course in each compound's signature region



Highest dose minus vehicle, mean ± SE across rats. %BOLD averaged over the listed atlas areas; each rat zeroed to its pre-injection mean; 30 s moving average. Shaded: analysis window. Dashed: injection. Panels compare timing, not magnitude: region sets differ in size and doses are not equipotent. LSD: 350-volume scan; males and females pooled.

DMT and 5-MeO-DMT reach their trough 3–4 min after injection and return toward baseline by 20 min, which is why they are mapped at the early window. Psilocybin's somatosensory signal rises within a minute and keeps climbing to 20 min. Ibogaine's thalamic signal builds over about 8 min and holds; mescaline's cerebellar suppression builds over about 10 min and holds. LSD's olfactory signal falls within a minute and stays about 3% below vehicle through 30 min. The shaded windows mark where each map was taken: at the peak for the fast tryptamines, on the plateau for the rest.

Conclusions

No single psychedelic signature. Psilocybin and ibogaine increase positive BOLD; LSD, mescaline, DMT and 5-MeO-DMT increase negative BOLD.

Timing separates the tryptamines. DMT and 5-MeO-DMT peak at 3–4 min and are back near baseline by 20 min; psilocybin and ibogaine rise slowly and are still near peak at 20 min; mescaline builds over 10 min and holds; LSD drops within a minute and holds for 30 min.

Where the change is strongest differs: cerebellum (mescaline), olfactory and prefrontal cortex (LSD), somatosensory cortex (psilocybin), thalamus and midbrain (ibogaine); DMT and 5-MeO-DMT suppress most of the forebrain.

Seeded connectivity expands under drug from the cerebellar nuclei (LSD, psilocybin at 0.03 mg/kg, mescaline) and from VTA/SN (ibogaine).

5-HT2A as the accelerator, the rest of each drug's pharmacology and kinetics as the steering. All but ibogaine are 5-HT2A agonists, yet no two maps match. Ketanserin pretreatment abolished psilocybin's positive BOLD response (unpublished), so that response is 5-HT2A-dependent; ibogaine, with no 5-HT2A agonism, has a map of its own.

Caveats: doses are not equipotent; per-area tests are uncorrected and read against chance; sexes pooled; LSD analyzed at a later window than the others.

Acknowledgments

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EKAM

NIH National Institute on Drug Abuse