Timing is everything: the whole-brain BOLD response to DMT in awake rats lasts minutes

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Introduction

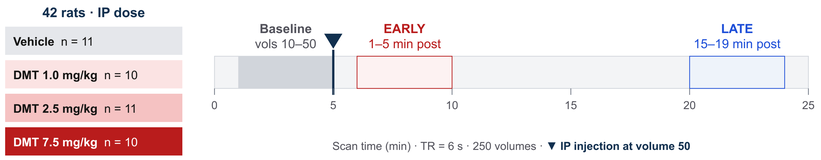
N,N-dimethyltryptamine (DMT) is the principal psychoactive constituent of ayahuasca and the psychedelic with the most compressed time course — in humans an intravenous dose peaks within about three minutes and resolves within fifteen. Our laboratory has characterised LSD, psilocybin, 5-MeO-DMT and mescaline in awake rats on this platform; each produced a dissociable whole-brain signature despite shared 5-HT2A agonism.

The 5-methoxy analogue is the direct precedent. Cavallaro et al. (2026) reported widespread negative BOLD in 123 of 166 regions during the first 10 min after IP 5-MeO-DMT, falling to only 14 of 166 at 11–20 min; somatosensory cortex diverged from vehicle within 1 min and had recovered by 13 min, after which positive BOLD exceeded vehicle.

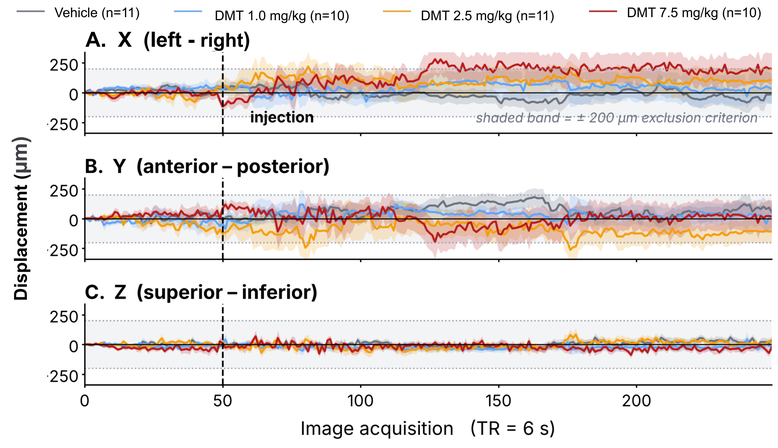
Because the response rises and falls within minutes, the acquisition window should determine what is measured. We tested this directly by analysing an early and a late window in the same scans.

Methods

- **Subjects.** 42 awake, head-restrained, drug-naive rats (23 M, 19 F), acclimated to restraint. One excluded for excessive motion.
- **Design.** Between-subjects. Vehicle (n=11), DMT fumarate 1.0 (n=10), 2.5 (n=11), 7.5 mg/kg (n=10), IP.
- **Acquisition.** BOLD phMRI, 250 volumes over 25 min (TR = 6 s); injection delivered remotely through an indwelling IP line at volume 50.
- **Windows.** EARLY = vols 60–100 (1–5 min post-injection) vs baseline 10–50. LATE = vols 200–240 (15–19 min), matching the acute and sustained windows of Cavallaro et al. (2026).
- **Segmentation.** 3D rat atlas; 165 regions common to all groups, grouped into 12 systems plus white matter.
- **Measure.** Positively and negatively activated voxels normalised to regional volume (% of ROI); regional time series.
- **Statistics.** Kruskal-Wallis; Mann-Whitney vs vehicle; Spearman rank correlation for ordered dose; Hedges' g; Benjamini-Hochberg FDR. Sex by two-way aligned rank transform ANOVA.



Motion control



Mean ± SEM displacement per acquisition in each orthogonal direction. Group means stay within the ±200 µm criterion in z throughout and in all three directions through the 1–5 min analysis window. Later drift appears in x at 7.5 mg/kg and in y at 2.5 mg/kg.

Volume-to-volume displacement rose with dose (mean FD 0.10 / 0.09 / 0.14 / 0.22 mm; ρ = +0.51, p = 0.0006), but only 7.5 mg/kg differed from vehicle (p = 0.005); 2.5 mg/kg did not (p = 0.24). Motion did not predict BOLD outcome in any group (all ρ < 0.21, n.s.), and adjusting for it strengthened the vehicle vs 2.5 mg/kg contrast (p = 0.024 → 0.010).

The response reverses between windows

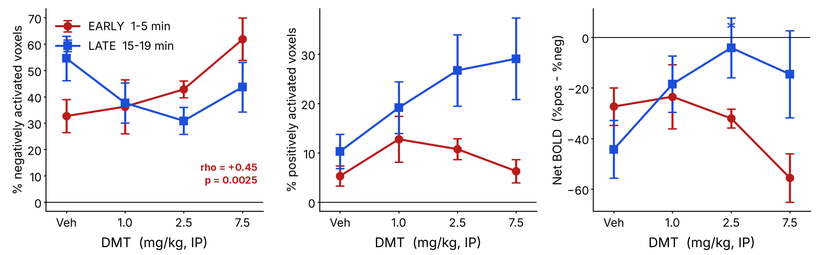


Figure 1. Whole-brain activation (mean ± SEM of 165 regions). Early (1–5 min), negative BOLD rises monotonically with dose; late (15–19 min), the relationship inverts and peaks at 2.5 mg/kg. *p < 0.05 vs vehicle.

EARLY (1–5 min) — suppression

Vehicle	32.7 ± 6.3
1.0 mg/kg	36.3 ± 6.7
2.5 mg/kg	42.9 ± 3.8
7.5 mg/kg	**61.9 ± 8.1**

% negative voxels. ρ = +0.45, p = 0.0025 · 7.5 vs veh p = 0.008, g = +1.21. 61 of 165 regions show a dose trend at FDR q < 0.05; 164 of 165 move the same way.

LATE (15–19 min) — recovery

Negative BOLD falls below vehicle and net BOLD shifts toward positive, maximally at 2.5 mg/kg (net −44.2% → −4.1%; p = 0.022, g = +1.00).

No region survives FDR for a monotonic dose trend in this window. The inverted-U dose response is a property of when the signal is sampled, not of the acute pharmacology.

Every system suppressed — then not at all

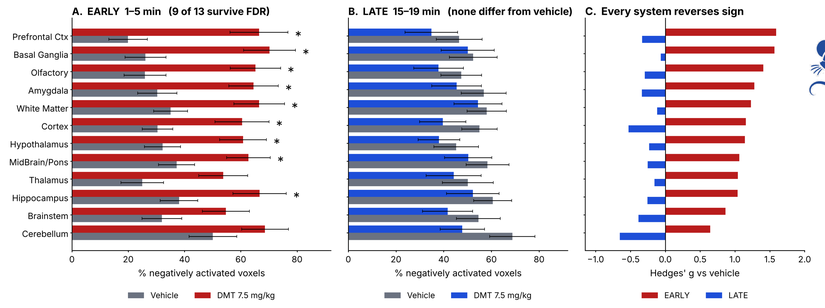


Figure 2. Negative BOLD by system, vehicle vs 7.5 mg/kg. (A) Early window: nine of 13 systems survive FDR (*q < 0.05); fold-change ranges from 3.3× in prefrontal cortex to 1.4× in cerebellum, and the regional pattern replicates across independent dose cohorts (ρ = 0.42–0.67). (B) Late window: no system differs from vehicle (smallest p = 0.17, all q > 0.80). (C) All 12 systems carry positive g early and negative g late — a complete sign reversal, with the anatomical ordering preserved.

No sex difference

No main effect of sex (early p = 0.36, late p = 0.32) and no dose × sex interaction (p = 0.47, p = 0.90) on any measure. Males were numerically higher at 7.5 mg/kg (72.4% vs 46.1%) but this did not reach significance (p = 0.17) and rested on one female with atypically low activation. With 4–6 animals per sex per dose, power was 0.28 for g = 1.0 — this design cannot resolve differences of the size reported previously for psilocybin and 5-MeO-DMT.

The same caution applies to connectivity

Resting-state scans in this protocol follow the phMRI series, covering roughly 20–40 min post-injection — entirely after the drug effect has resolved. Connectivity measured in that window reflects the post-acute state, not the psychedelic one, and should not be read as an absence of acute network change. Human DMT imaging captures the first 20 min, with the subjective peak at 2–5 min (Timmermann et al., 2023). Acute connectivity requires acquisition within the first 10 min.

Second-by-second: basal ganglia

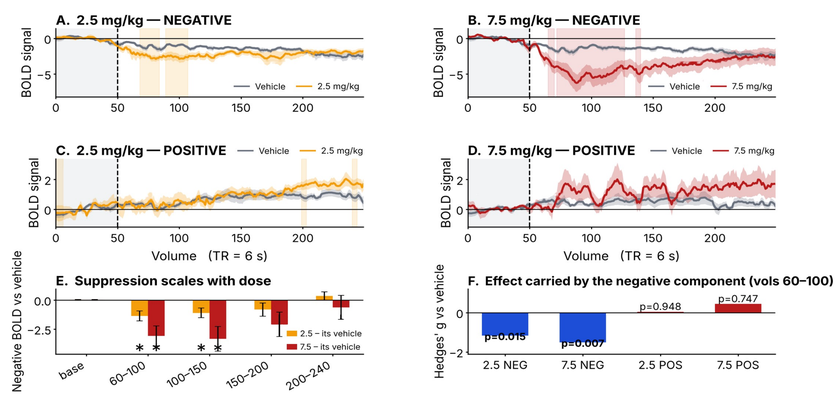


Figure 3. Composite of 11 basal ganglia regions, each dose against its own vehicle. Baselines do not differ. Shading marks p < 0.05. At 7.5 mg/kg the effect begins ~1.5 min after injection, peaks at −4.75 at 3.9 min, remains significant to ~9 min and converges with vehicle by ~10 min; 72 of 250 volumes reach p < 0.05 (≈13 expected by chance).

Suppression is dose-ordered: at volumes 60–100 the negative component falls 1.4 units below vehicle at 2.5 mg/kg (g = −1.17, p = 0.015) and 3.1 units at 7.5 mg/kg (g = −1.52, p = 0.007). All 11 regions survive FDR at 7.5 mg/kg.

The positive component is unchanged at both doses (g = +0.04 and +0.44; p = 0.95 and 0.75). A single vasoactive mechanism would be expected to move both components.

Conclusions

1. DMT produces dose-dependent, brain-wide negative BOLD within 1–5 min of IP injection, rising monotonically across 1.0–7.5 mg/kg — the same acute negative-BOLD signature reported for 5-MeO-DMT.
2. Time-resolved data place the effect at onset ~1.5 min, peak ~4 min, resolution by ~10 min — matching the rapid onset and offset of DMT in humans, and closely paralleling 5-MeO-DMT (Cavallaro et al., 2026).
3. By 15–19 min the response has reversed in every one of 12 systems, with none differing from vehicle; net BOLD shifts positive, peaking at 2.5 mg/kg.
4. Suppression is not spatially uniform: system fold-change varies 2.4-fold and the regional pattern replicates across independent cohorts, indicating neuronally patterned rather than purely vascular action.
5. No sex difference was detected in either window; the study was not powered for this comparison.
6. Methodological implication. For short-acting tryptamines, both activation and connectivity must be sampled inside the window of drug action.

Acknowledgements

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Disclosures. CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging.

References. Cavallaro N et al. Neuropharmacology 291:110886, 2026 · Fuini E et al. Front Neurosci 19:1554049, 2025 · Ghaw A et al. Brain Commun 6:fcae194, 2024 · Timmermann C et al. PNAS 120:e2218949120, 2023.

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