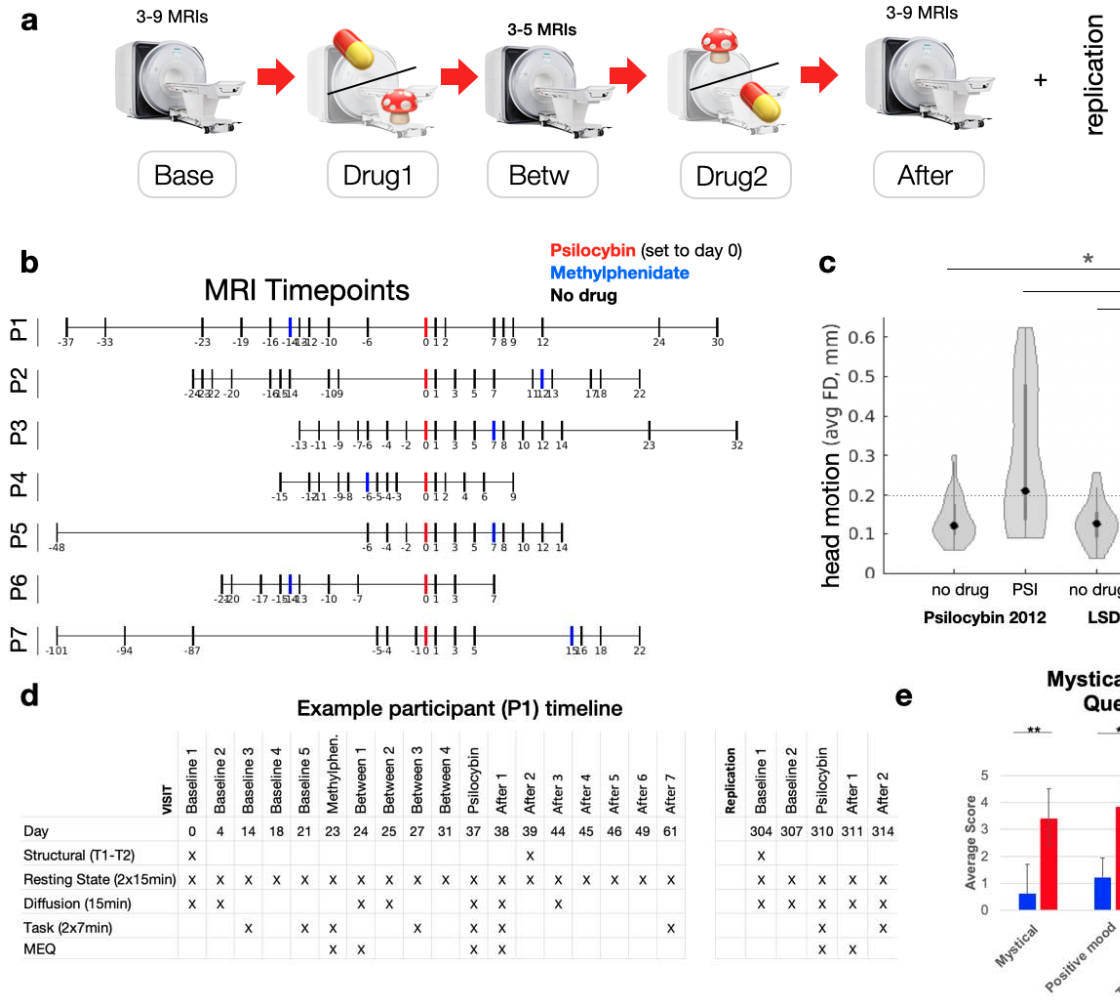
Tables S1

Participant	P1	P2	P3	P4	P5	P6	P7
Basic demographics							
Gender (n=3 females)	Male	Male	Female	Female	Male	Female	Male
Age Range (years)	41-45	36-40	36-40	36-40	18-20	21-25	41-45
Last degree completed	Bachelor's	Bachelor's	Bachelor's	Graduate	High School	Bachelor's	Graduate
Last psychedelic exposure (months)	24	24	12	24	24	12	60
Replication protocol (days between doses)	Yes (273 days)	No	Yes (349 days)	Yes (350 days)	Yes (300 days)	No	No
Mini-International Personality Item Pool (Mini-IPIP)							
Neuroticism	3	2.5	2.75	2	2	1.25	2.5
Extraversion	2	3.5	3.25	3.25	4	3	3.5
Openness	2.5	3.75	1.75	4.75	4	5	3.75
Agreeableness	3.75	4.25	2.5	4.5	4	4.5	4.25
Conscientiousness	3	1.75	3	4.25	3.75	2.5	1.75
MRI data obtained							
Number of usable 15-minute rsfMRI scans, without PSIL	53	44	40	44	41	26	17
Number of usable 15-minute rsfMRI scans, on PSIL	8	0	5	5	7	2	3
Total task MRI	9	9	7	9	3	6	16
Number of diffusion MRI, without PSIL	12	12	12	16	16	16	8
Number of diffusion MRI, on PSIL	2	0	2	2	2	0	0
Other protocol aspects							
Respirations and pulse acquired	Partial*	No	Partial*	Yes	Yes	Yes	Yes
Completed replication protocol	Yes	No	Yes	Yes	Yes	Yes	No

Table S1. Participant demographics and neuropsychological assessments

Figure S1



VISIT	Baseline 1	Baseline 2	Baseline 3	Baseline 4	Baseline 5	Methylphen.	Between 1	Between 2	Between 3	Between 4	Psilocybin	After 1	After 2	After 3	After 4	After 5	After 6	After 7
Day	0	4	14	18	21	23	24	25	27	31	37	38	39	44	45	46	49	61
Structural (T1-T2)	x												x					
Resting State (2x15min)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diffusion (15min)	x	x					x	x			x	x		x				
Task (2x7min)			x		x	x			x		x	x						x
MEQ						x	x				x	x						

Replication	Baseline 1	Baseline 2	Psilocybin	After 1	After 2
	304	307	310	311	314
	x				
	x	x	x	x	x
	x	x	x	x	x
			x		x
			x	x	

Figure S1. Quantifying Psilocybin effects with Precision Functional Mapping: design. *a) Schematic illustrating the design of the precision functional mapping study of acute and persisting effects of psilocybin. Bringing participants in for multiple baseline visits enabled high-fidelity individual brain mapping, measurement of day-to-day variance, and acclimation to the scanner. b) Timeline of imaging visit for 7 subjects. c) Head motion comparison across datasets. Average head motion (FD, in mm) off and on drug is compared between our dataset and prior psychedelic fMRI studies (Carhart-Harris et al., 2012 & 2016). Dotted line at 0.2mm = recommended cutoff for usable fMRI scans. Asterisk: p<0.05, t-test. d) Timeline for an example participant. e) Participants reported significantly higher scores on all dimensions of the mystical experience questionnaire during psilocybin than placebo.*

Figure S2

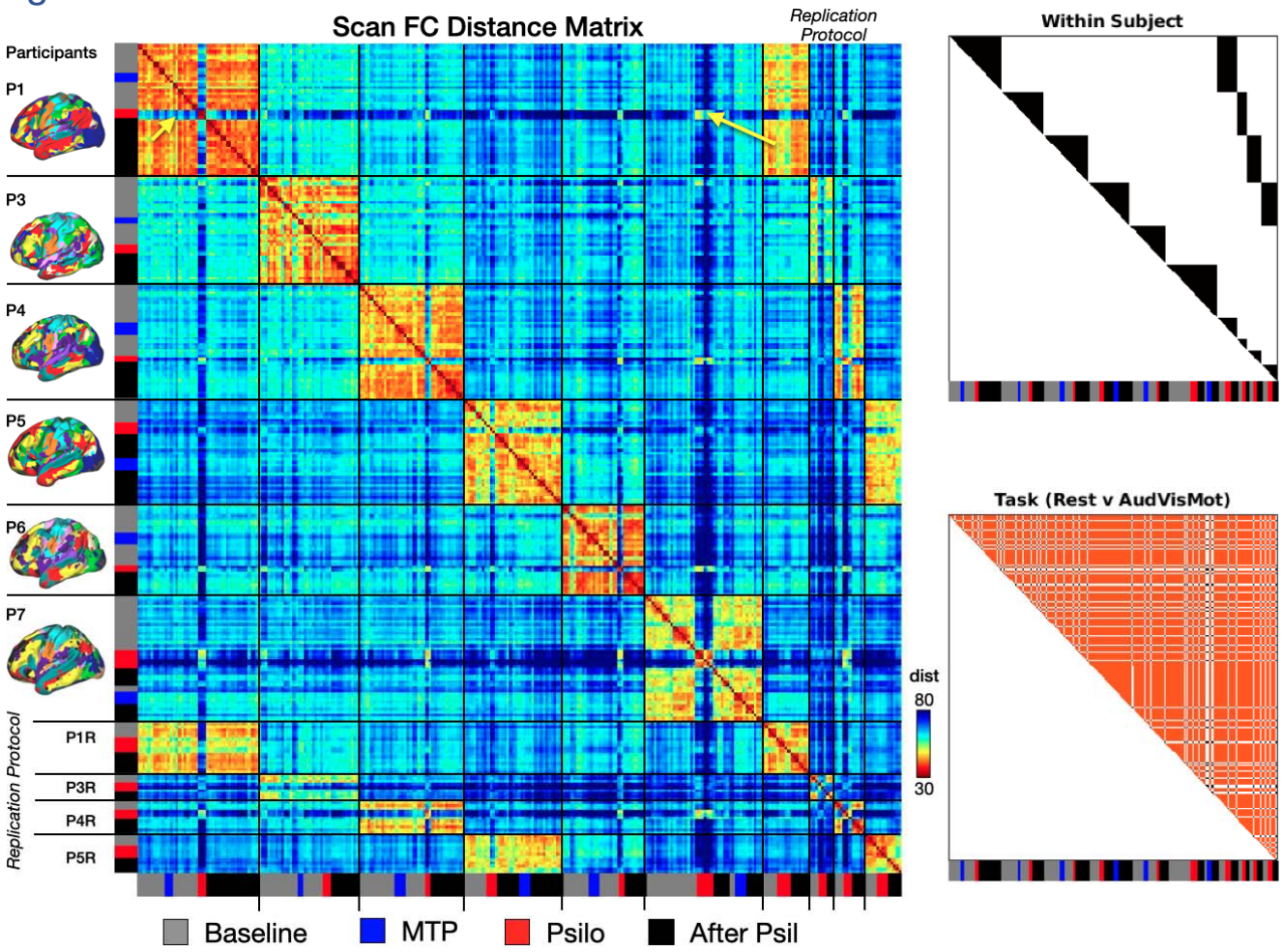


Figure S2. FC Distance and condition matrices. *Following Gratton et al., 2018, we compare between rsfMRI sessions in order to quantify contributors to variability in functional brain networks. In this approach, the effects of group, individual, session, and drug (as well as their interactions) are examined by first calculating the Euclidian distance among every pair of functional network matrices (i.e., distance among the linearized upper triangles). LEFT: the resulting second-order 'distance matrix'. Each row and column are brain networks from a single study visit. The values in the matrix indicate distance of functional networks between a pair of visits (i.e., Euclidean distance between the linearized upper triangles of two FC matrices). RIGHT: visualization of how the distance matrix was subdivided to compare different contributors to network change (typically relative to baseline scans). TOP: Black triages are separate subjects. Replication protocol visits are listed at the end. Note that psilocybin sessions (e.g. magenta arrow pointing to PS18 Psilocybin) are less similar to no-drug days, but more similar to psilocybin sessions from others, or in the same individual >6 months late*

Figure S3

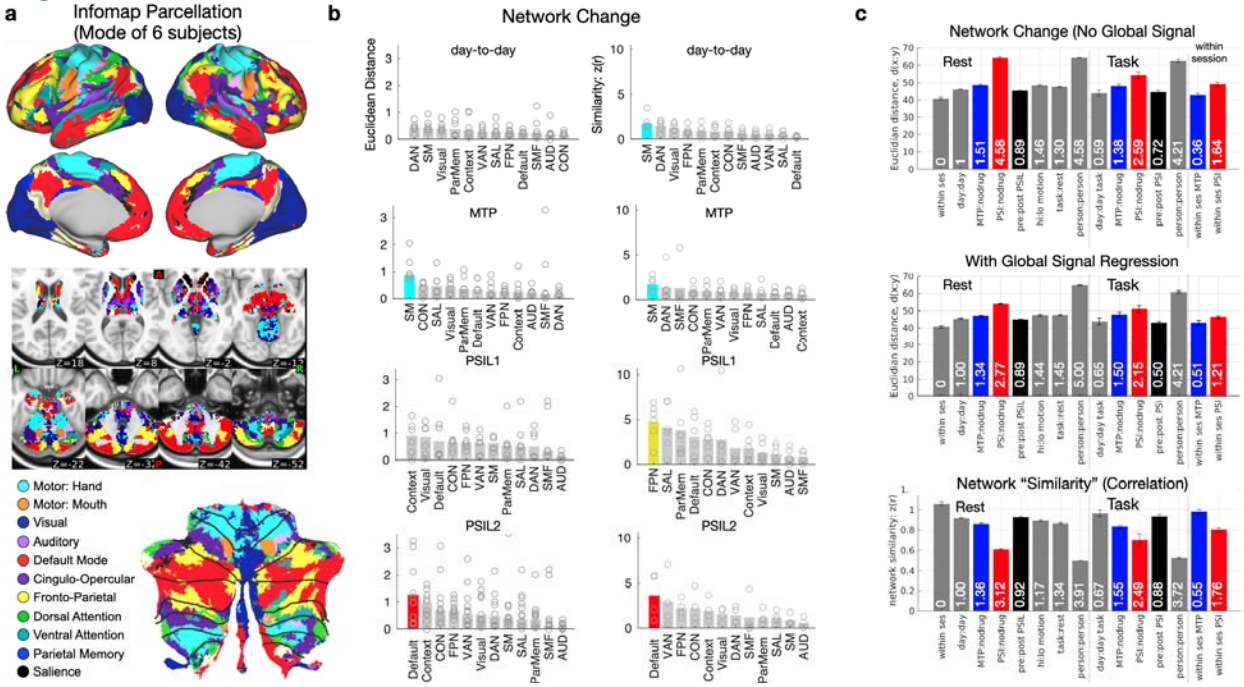


Figure S3. Network change compared across different conditions, brain structures, and measures. **a)** Mode Infomap-based RSN parcellations. b) Network selectivity of psilocybin-associated cortical change is assessed for different conditions (and separately for psilocybin initial and replication doses). Left column of bar plots shows network change based on Euclidean distance, right column is based on [decrease in] Pearson correlation. Colored bars indicates that the network showed change values that were above chance based on permutation of network labels ($p<0.05$, 10,000 null rotation). c) Network Change, defined as the average Euclidean distance between vectorized FC matrices, was examined before (top) and after (bottom) global signal regression that were (1) from the same individual within a single session, (2) from the same individual across days (''day:day''), (3) from the same subject but different drug states (e.g. ''psil:no-drug''), (4) from the same individual but different tasks (''task:rest''), (5) from the same individual between highest motion scans and baseline, (6) from different individuals (''person:person''). Bottom: Network change was also calculated using ''similarity'' (Pearson correlation) rather than difference, and yielded similar results.

Figure S4

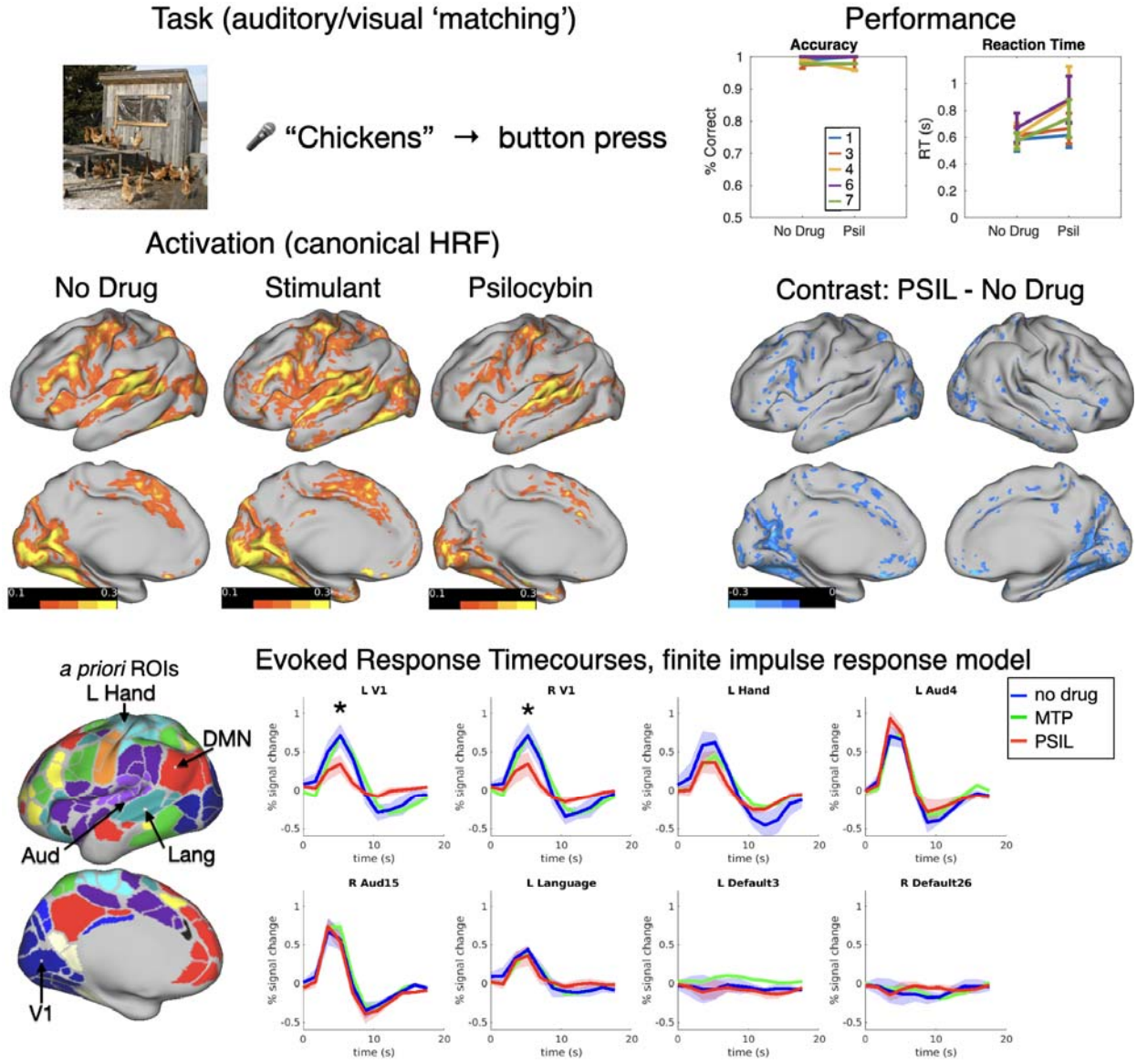


Figure S4. Auditory-Visual-Motor task. *Top: Visualization of task design. Top right: psilocybin shows no effect on performance (both are at ceiling), but shows increase in RT latency and RT variability. Middle: Activation maps (left, beta weights) and contrasts (right, simple subtraction) using canonical HDR. Bottom: Average timecourses in 8 a priori regions of interest, calculated using FIR model. * P<0.05, ANOVA of Condition x HRF Betas (Main effect of all trials).*

Figure S5

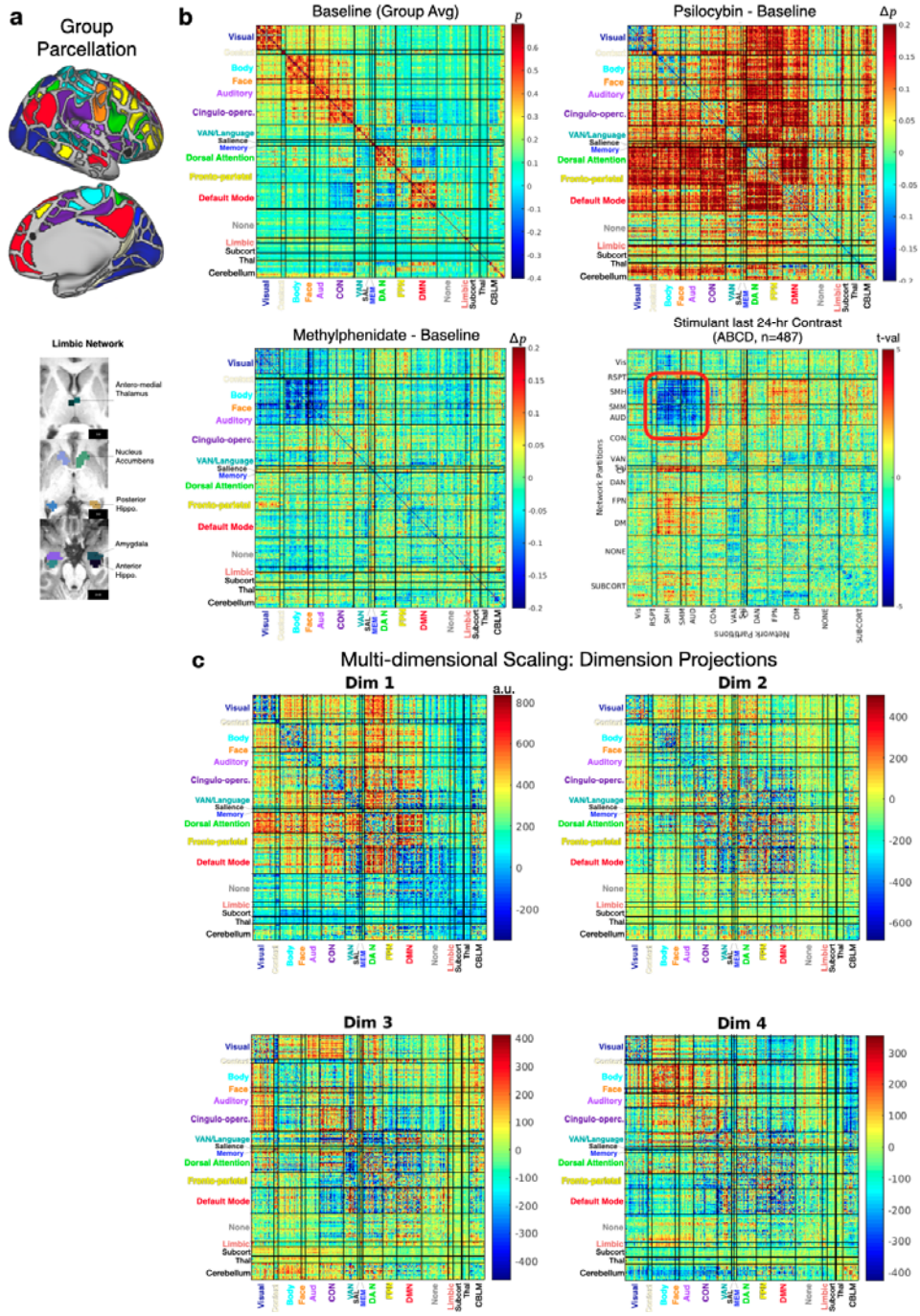


Figure S5. FC Matrices using Gordon-Laumann Parcellation. Top: Parcels and Average Condition FC Matrices. *Top right: Psilocybin increases the correlation between Dorsal attention, Fronto-parietal, and Default Mode network to each other and to other cortical, limbic, and cerebellar systems. Top left: The group average FC 'adjacency' matrix, Bottom left: Methylphenidate minus baseline, Bottom right: for comparison and validation, we compared methylphenidate to the main effect of stimulant use within the last 24 hours (n=487 yes, n=8000 no) in ABCD fMRI data. B) Weights from the first 6 dimensions generated by multi-dimensional scaling of the full dataset. Dimension 1 shows strong acute psilocybin effect, dimension 4 shows weak pre-post psilocybin effect.*

Figure S6

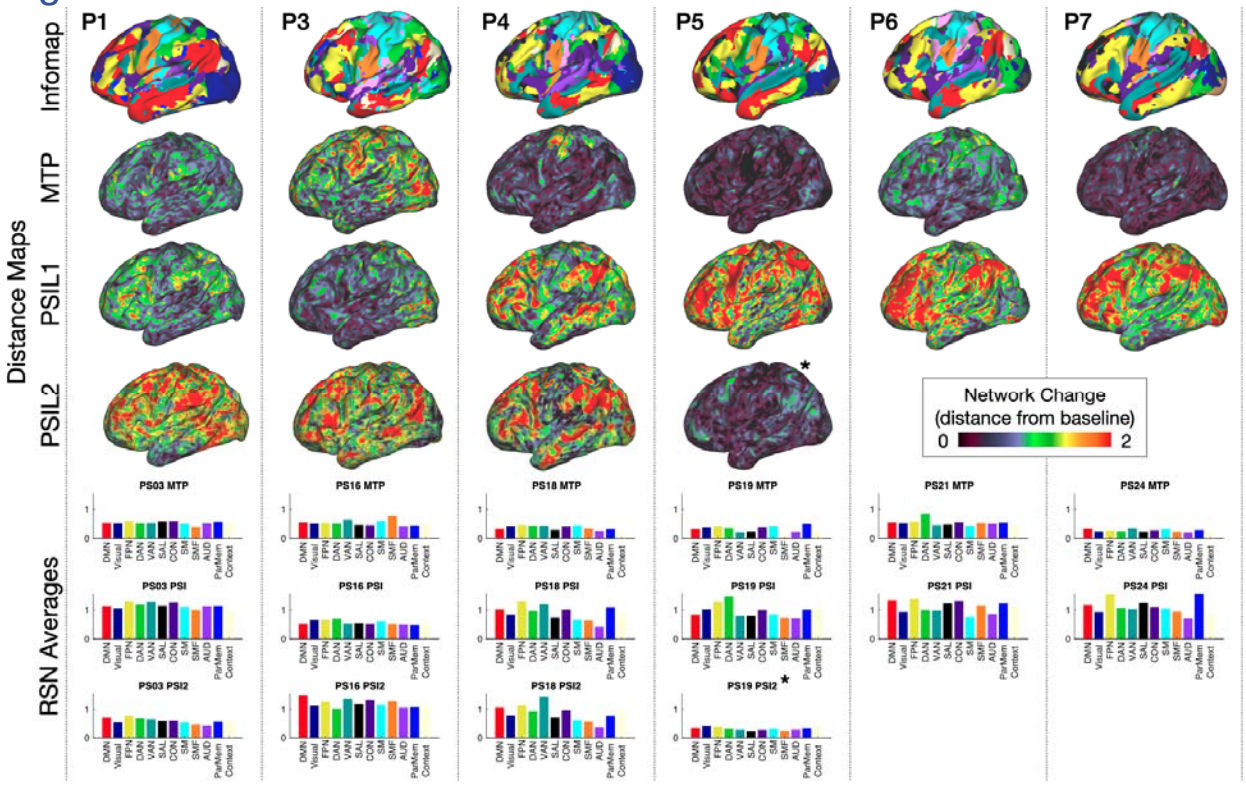


Figure S6. Individual subject MTP and PSIL Network Change maps. *Top: Individual subject infomap parcellations. Middle: Network change maps, generated by calculating Euclidean distance from baseline seedmaps for each vertex. *Sub5 had an episode of emesis 30 minutes after drug ingestion during PSIL2. Bottom: Averaging distance maps within RSN generates RSN average network change scores (combined to map Fig. 1c).*

Figure S7

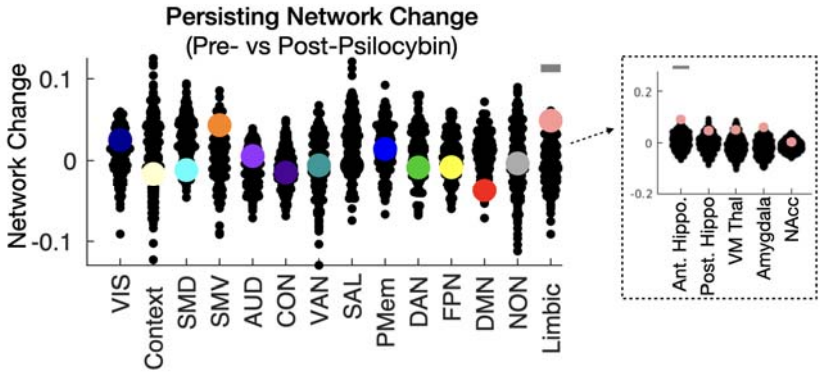


Figure S7. Pre/Post Psilocybin Network Change Analysis . *Left: Permutation testing of persisting effects by system. Colored dots indicate network change for each system (baseline versus all post-psilocybin sessions). Black dots indicate network change for 500 permutations of pre/post labels. The gray bar above Limbic system indicates that persisting after psilocybin ($p<0.05$). Right: post-hoc analysis of the five bilateral regions of interest comprising the limbic system - anterior hippocampus, posterior hippocampus, ventromedial thalamus, amygdala, and nucleus accumbens. VIS = visual, SMD = somato-motor dorsal, SMV = somato-motor ventral, AUD = auditory, CON = cingulo-opercular network, VAN = ventral attention network, SAL = salience, PMem = parietal memory, DAN = dorsal attention network, FPN = fronto-parietal network, DMN = default mode network, NON = unassigned/low signal.*