Acute Functional Brain Changes Associated with Psilocybin in Healthy Adults and Depression: A systematic review and meta-analysis

Joshua M. Poulin[1,2], Nic Viulet[1], Ashley Liu[1], Bradley J. MacIntosh[1,3†], Sean M. Nestor[1,2,4†]

Contact: josh.poulin@mail.utoronto.ca

† Co-Senior authors

1) Hurvitz Brain Sciences Program, Sunnybrook Research Institute; 2) Institute of Medical Science, University of Toronto; 3) Department of Medical Biophysics, University of Toronto 4) Department of Psychiatry, University of Toronto

Background

- **Psilocybin** is a naturally occurring serotonergic psychedelic compound found in mushrooms of the *Psilocybe* genus that has recently emerged as a promising rapid-acting treatment for **Major Depressive Disorder** (MDD) with a favourable safety profile and robust efficacy in alleviating depression symptoms.[1-5]
- Previous studies have begun to uncover its therapeutic mechanisms of action on brain function and sustained alterations in brain network activity.[4,5]
- There have been no systematic reviews that have comprehensively synthesized the results from neuroimaging studies to identify trends and consistent patterns of psilocybin-induced changes in mood brain network activity.

Objective: To conduct a systematic review and coordinate-based meta-analysis of changes in mood-related brain network activity following psilocybin administration in healthy adults and adults with MDD.

Methods

- Using OVID search engine, a systematic literature search was conducted on EMBASE, MEDLINE, CENTRAL, and PsycINFO up to present day.
- The search strategy and terms were developed with the population, intervention, comparison, and outcomes (PICO) framework.[6]
- Along with our inclusion and exclusion criteria (**Table 1**), the search included neuroimaging studies examining psilocybin's effects in healthy adults, focusing on pre- and post-psilocybin treatment multi-modal regional and network brain activation data with corresponding MNI or Talairach coordinates, if available.

Table 1: Inclusion/Exclusion Criteria

Inclusion	Exclusion
Adults aged 18 years or older, either healthy or with depression	Protocols
Randomized controlled trials (RCTs) and quasi-experimental studies with neuroimaging	Non-experimental studies
Imaging modalities: • fMRI including ASL-fMRI and BOLD-fMRI techniques • EEG • SPECT • PET	Discussion or review papers
Peer-reviewed articles	

- Reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]
- The literature search was conducted on February 10, 2025, identifying 1577 studies from the database search.
- Full-text screening identified 14 studies (**Table 2**) that met eligibility criteria and were included in the analysis, with a total of 364 participants (52 participants with MDD and 310 healthy adults). 26 studies require contacting the authors, and 31 studies are left to undergo full-text review.

Preliminary Results

Table 2: Characteristics of Included Studies

	Study	Sample Size (female)	Mean Age (SD)	Age Range	Psilocybin Dose	Psilocybin Schedule	Depression Measure	Depression Type	Modality	Imaging Pre and Post Timeline	Rest or Task
MDD_1	Wall et al., 2023	19(6)	41.3(10.5)	27-64	10 mg, 25 mg	Two sessions one week apart	QIDS; BDI; HAMD (21-item)	TRD	fMRI; ALFF	pre: 1 week before first treatment; post: +24 hours after second treatment	task-based: music listening post-dose
MDD_2	Roseman et al., 2018	19(6)	44.7(10.9)	27-64	10mg, 25mg	Two sessions one week apart	HAMD (21-item)	MDD	BOLD-fMRI	pre: 1 week before first treatment; Post: morning after second treatment => Both @ 10am	task-based: emotional faces images task
MDD_3	Carhart-Harris et al. 2017	16(4)	42.8(10.1)	N/A	10 mg, 25mg	Two sessions one week apart	QIDS-SR16	TRD	ASL; BOLD-fMRI	pre: before baseline; post: +24 hours after second treatment	rest

	Study	Sample Size (female)	Mean Age (SD)	Age Range	Psilocybin Dose	Schedule	Placebo or Comparator	Modality	Imaging Pre and Post Timeline	Rest or Task
HC_1	Smigielski et al., 2019	38(15)	51.66(8.32)	N/A	315 µg/kg body weight; absolute dose, 21.82(3.7) mg	administered on the fourth day of the 5-day retreat	lactose	fMRI	pre: -24 hours a 5-day retreat; post: +24 hours a 5-day retreat	task: open awareness meditation
HC_2	Stoliker et al., 2024	24(11)	26.3	20-40	0.2 mg/kg body weight, oral	Two sessions two weeks apart	179 mg mannitol and 1 mg colloidal silicon dioxide	fMRI	post: +70 minutes following administration	rest
HC_3	McCulloch et al., 2021	10(4)	28.3(3.4)	N/A	0.2-0.3 mg/kg	One session approximately two weeks after baseline	None	BOLD-fMRI and [11C]Cimbi-36 PET	pre: fMRI baseline and PET baseline; post: fMRI 1 week and 3 months, PET 1 week	rest
HC_4	Siegel et al., 2024	7(3)	N/A	18-45	25 mg	administered 1-2 weeks post-methylphenidate	40 mg methylphenidate	BOLD-fMRI	pre: 9 fMRIs baseline and post-methylphenidate; post: 3-5 fMRIs following psilocybin	rest and task: perceptual (matching)
HC_5	Mason et al., 2020	60(25)	22.73(2.90)	18-40	0.17 mg/kg, oral, in powder form with bitter lemon	Single session	bitter lemon	fMRI	post: MRI +50 minutes following administration, single-voxel proton MRS in the mPFC (+65 minutes) and hippocampus (+95 minutes) following administration, and fMRI +102 minutes following administration	rest
HC_6	Kraehenmann et al., 2015	25(9)	24.2(3.42)	N/A	0.16 mg/kg, oral	Two sessions at least 14 days apart	lactose	fMRI	post: 70 to 90 minutes following administration	task: amygdala reactivity task; simple motor task
HC_7	Barrett et al., 2020	12(7)	32.1(7.5)	18-45	25mg/70kg	Single session	None	fMRI	pre: one day before administration; post: one week and one month following administration	rest and task: emotion tasks
HC_8	Duerler et al., 2021	15(5)	26.86	20-40	0.2mg/kg, oral	Two sessions two weeks apart	179 mg mannitol and 1 mg colloidal silicon dioxide	EEG-fMRI	post: +85 minutes following administration	task: roving somatosensory oddball
HC_9	Madsen et al., 2021	15(6)	34.3(9.8)	N/A	0.2-0.3 mg/kg, oral	Single session	Non-psychedelic drug	fMRI	pre: before psilocybin; post: +40, 80, 130, and 300 minutes following administration	rest
HC_10	Rieser et al., 2023	70(29)	25.33(3.91)	N/A	0.16 mg/kg n =31, 0.2 mg/kg n = 10, 0.215 mg/kg n = 29	Two sessions 10 days apart	100% lactose n = 31, 179 mg mannitol and 1 mg aerosil (placebo)	BOLD-fMRI; ASL	post: fMRI +60 minutes following administration, ASL +80-100 minutes following administration	rest
HC_11	Muthukumaraswamy et al., 2013	15	34.5(2.3)	N/A	2 mg in 10 mL of saline	Single session	10 mL saline placebo	MEG	pre: -5 minutes before infusion; post: +5 following infusion	rest and task: visuomotor stimulation

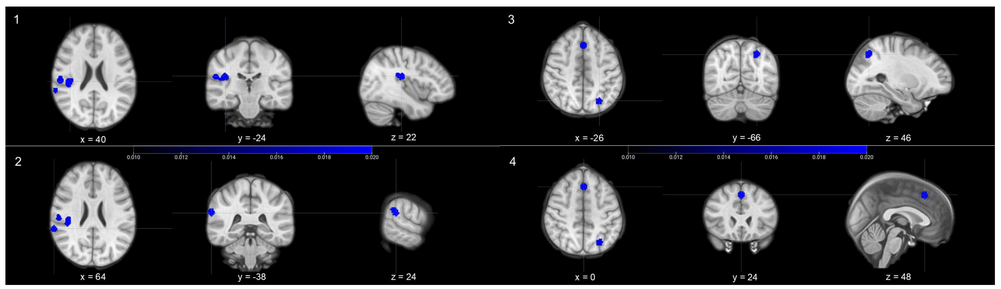
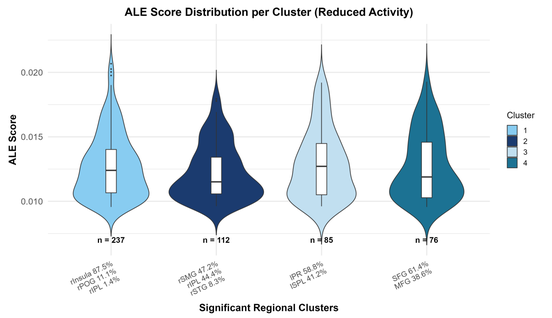
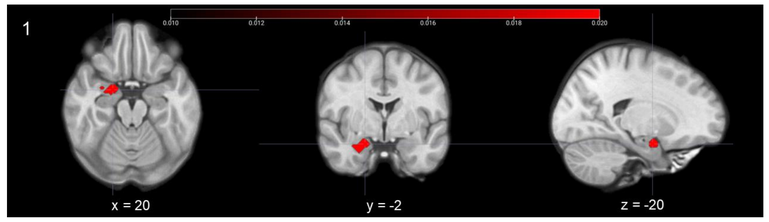


Figure 1. Pooled MDD+HC Condition Reduced Activity. **Top row**: Activation Likelihood Estimation (ALE)-derived clusters of significantly reduced activation overlaid on MNI152 atlas. **Bottom row**: Voxel-wise distribution of ALE scores for each significant cluster. Higher ALE scores (e.g., > 0.01) indicate greater convergence in reported foci across studies. Only voxels surviving cluster-level correction ($p < 0.05$, FWE-corrected) are included**.** Cluster labels denote anatomical regions: POG: Postcentral Gyrus; IPL: Inferior Parietal Lobule, SMG: Supramarginal Gyrus; STG: Superior Temporal Gyrus; PR: Precuneus; SPL: Superior Parietal Lobule; SFG: Superior Frontal Gyrus; MFG: Medial Frontal Gyrus.





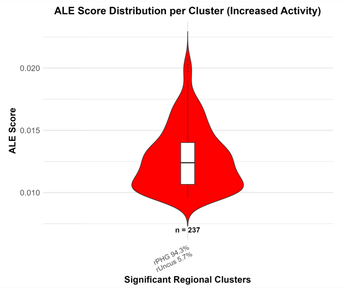


Figure 2. Pooled MDD+HC Condition Increased Activity. **Top row**: ALE-derived clusters of significantly increased activation overlaid on MNI152 atlas. **Bottom row**: Voxel-wise distribution of ALE scores for each significant cluster. Higher ALE scores (e.g., > 0.01) indicate greater convergence in reported foci across studies. Only voxels surviving cluster-level correction ($p < 0.05$, FWE-corrected) are included**.** Cluster labels denote anatomical regions: PHG: Parahippocampal Gyrus.

Discussion

- Significant clusters of convergent activation identified in limbic, sub-lobar, parietal, and frontal regions.
- Decreased activity spanned areas within the right insula, parietal (rIPL, rSMG, rPOG), and frontal regions (SFG, MFG) (**Figure 1**), implicated in the salience (SN), somatosensory, default mode (DMN), and central executive networks.
  - Conversely, studies have reported hyperactivity in the insula, PCG, PR, and SPL, along with increased functional coupling between the DMN and SN in MDD patients.[8-10]
- Two limbic structures (rPHG and rUncus) showed increased activation (**Figure 2**), critical for their roles in emotion, memory, mood regulation, affect processing, and fear conditioning.[11-13]

Limitations

- This review is ongoing, and the findings presented are preliminary as they are based on a subset of included experiments.
- Activation likelihood estimation identifies spatial convergence yet does not measure effect size or connectivity.
- Planned contrast analyses between MDD and healthy control groups cannot be performed at this stage due to an insufficient number of experiments per condition.

References

1. von Rotz R, Schindowski EM, Jungwirth J, Schuldt A, Rieser NM, Zahoranszky K, et al. Single-dose psilocybin-assisted therapy in major depressive disorder: A placebo-controlled, double-blind, randomised clinical trial. EClinicalMedicine. 2023 Feb;56:101809.
2. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. N Engl J Med. 2022 Nov 3;387(18):1637–48.
3. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of Psilocybin versus Escitalopram for Depression. N Engl J Med. 2021 Apr 15;384(15):1402–11.
4. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol. 2008 Aug;22(6):603–20.
5. Studerus E, Kometer M, Hasler F, Vollenweider FX. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. J Psychopharmacol. 2011 Nov;25(11):1434–52.
6. Eriksen MB, Frandsen TF. The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. J Med Libr Assoc. 2018 Oct;106(4):420–31.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.
8. Wu D, Li J, Wang J. Altered neural activities during emotion regulation in depression: a meta-analysis. J Psychiatry Neurosci. 2024;49(5):E334–44.
9. Wang W, Zhou E, Nie Z, Deng Z, Gong Q, Ma S, et al. Exploring mechanisms of anhedonia in depression through neuroimaging and data-driven approaches. J Affect Disord. 2024 Oct 15;363:409–19.
10. Cheng W, Rolls ET, Qiu J, Yang D, Ruan H, Wei D, et al. Functional Connectivity of the Precuneus in Unmedicated Patients With Depression. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 Dec;3(12):1040–9.
11. Grégoire L, Robinson TD, Choi JM, Greening SG. Conscious expectancy rather than associative strength elicits brain activity during single-cue fear conditioning. Soc Cogn Affect Neurosci. 2023 Oct 24;18(1).
12. Janiri D, Moser DA, Doucet GE, Luber MJ, Rasgon A, Lee WH, et al. Shared Neural Phenotypes for Mood and Anxiety Disorders: A Meta-analysis of 226 Task-Related Functional Imaging Studies. JAMA Psychiatry. 2020 Feb 1;77(2):172–9.
13. Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain. 2013 Jun;136(Pt 6):1692–707.