

The PLASTICITY Trial: Protocol and Design of a Double-Blind Dose-Response Study of Psilocybin in Cognitively Normal Older Adults

Tyler N. Toueg^{1,2,3}, Ava Axelrod³, Tyrone J. Sgambati³, Sean Noah^{1,2,3}, Rachel Su^{1,3}, Catriona Miller^{3,4}, Brian Anderson^{3,4}, Dacher Keltner^{3,5}, William J. Jagust^{1,2}, Michael A. Silver^{1,2,3,6}

¹Department of Neuroscience, University of California, Berkeley, ²Helen Wills Neuroscience Institute, University of California, Berkeley, ³UC Berkeley Center for the Science of Psychedelics, University of California, Berkeley, ⁴University of California, San Francisco, ⁵Department of Psychology, University of California, Berkeley, ⁶Herbert Wertheim School of Optometry and Vision Science, University of California, Berkeley

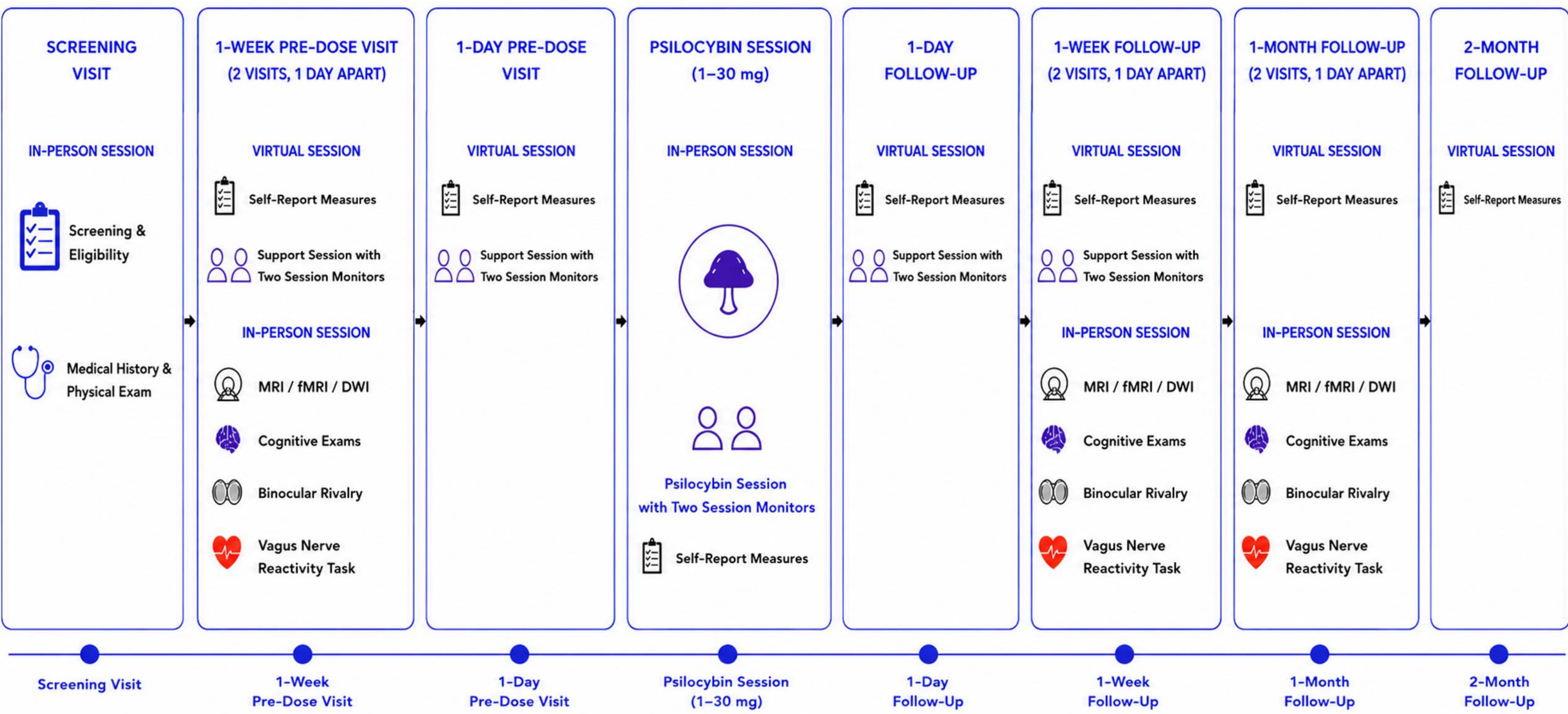
Contact: ttoueg@berkeley.edu

Introduction

- Both brain aging and Alzheimer’s disease are associated with synaptic alterations, driving an urgent need for new strategies to promote successful aging.
- Psilocybin may hold promise as a novel intervention, as preclinical studies have demonstrated increases in synaptic density in the hippocampus and prefrontal cortex, and human studies have shown beneficial effects on psychological outcomes relevant for cognitive aging.
- Despite a growing body of psychedelic research in various populations, older adults are underrepresented, comprising less than 1.4% of all participants.
- The Psychedelic Longitudinal Aging Study In Cognitively Healthy Older Adults (PLASTICITY) addresses this critical gap as the first psychedelic neuroimaging study of older adults (NCT06367738).
- PLASTICITY will evaluate whether psilocybin promotes changes in brain microstructure and psychological outcomes that are relevant for cognitive decline and successful aging.

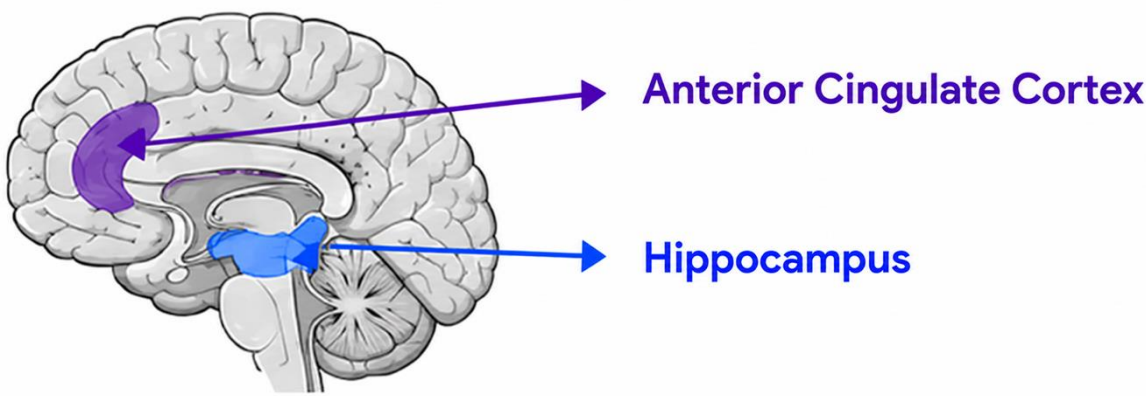
Methods

Trial Design



Primary Outcome

Within-subject, dose-dependent decrease in mean diffusivity in hippocampus and anterior cingulate cortex from baseline to 1-week post-dose using ZOOMit DWI



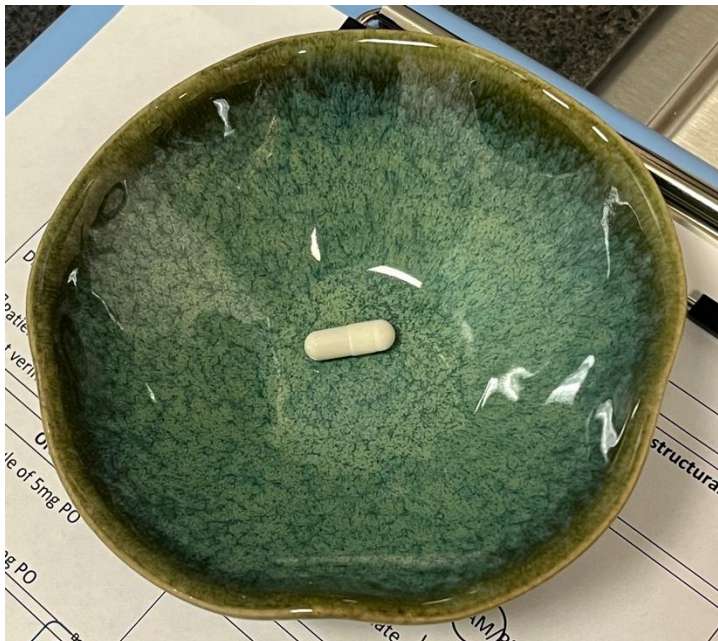
Key Secondary Outcomes

Within-subject, dose-dependent change in:

- ↓ Repetitive Negative Thinking (PTQ)
- ↓ Perceived Stress (PSS)
- ↓ Apathy (AES)
- ↓ Neuroticism (BFI-2-XS)
- ↑ Social Connectedness (SCS-R)
- ↑ Resilience (BRS)
- ↑ Purpose in Life (PWB-PIL)
- ↑ Emotion Regulation (ERQ)

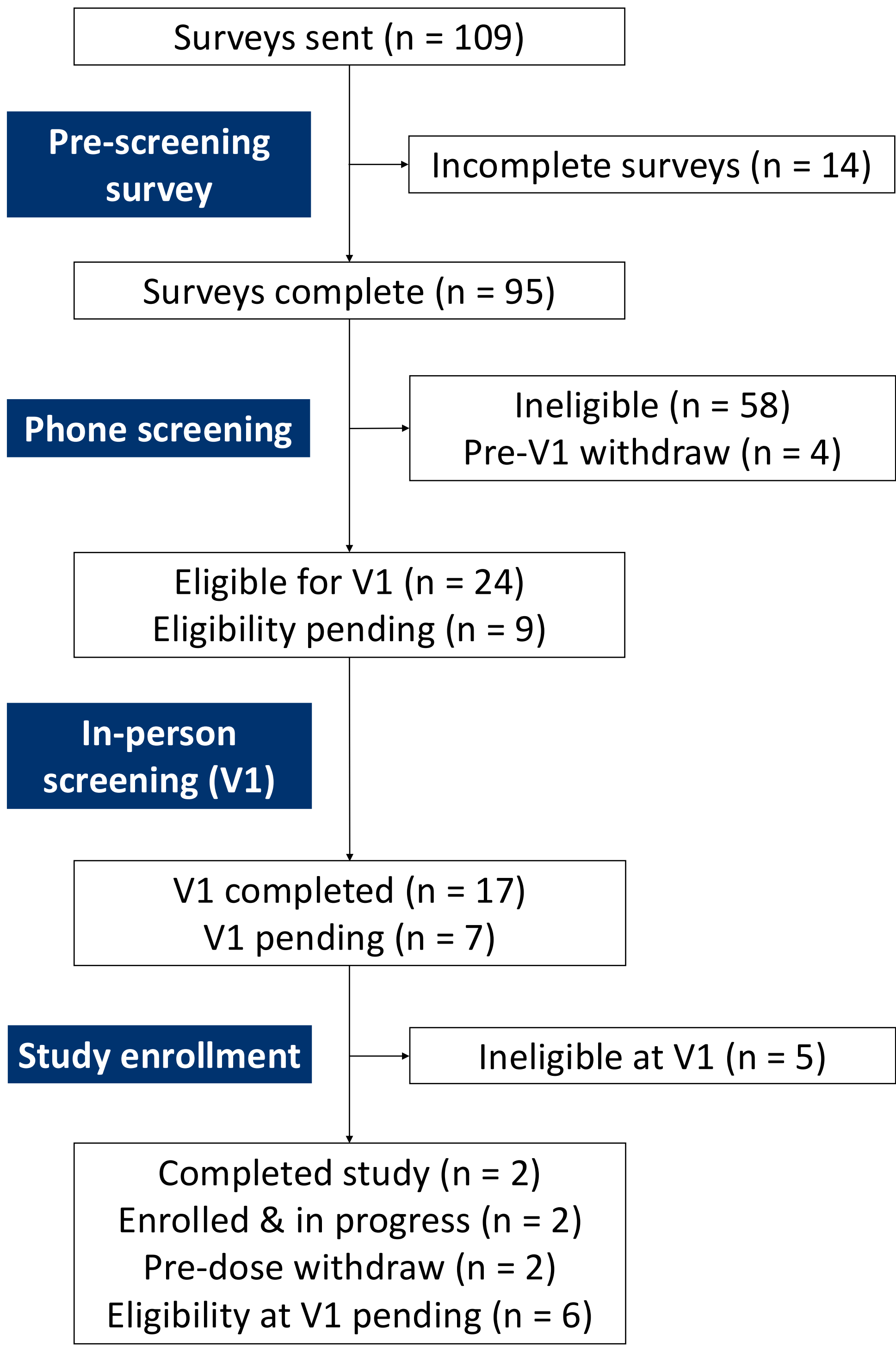
Key Inclusion Criteria

- Inclusion criteria include age 60-85
- Normal cognitive functioning
- No major psychiatric, neurological or cardiovascular disorders
- No recent psychedelic, entactogen, or dissociative drug use
- No motor impairment



Results

Recruitment & Enrollment Summary



Most common reasons for ineligibility

- Pre-screening = exceed lifetime psychedelic use
- In-person screening (V1) = uncontrolled hypertension

“I was just reminded of my responsibility to share more with my loved ones ... how much I appreciate them. I know that I feel it, but I don’t express it out as much ... I was kind of being reminded of that in a very visceral way ... I think that will be something that will stay with me”

Adverse Events Summary

- In all subjects to date (n = 3), no serious adverse events have been reported.
- All reported adverse events have been mild or moderate severity.

	AE Organ Class	AE Term	Related to Study Drug?
S1	Psychiatric disorders (3)	Perceptual distortion: visual	Definitely
		Sadness	Probably
		Tearfulness	Probably
	Vascular disorders (2)	Lightheadedness	Probably
		Nausea	Probably
S2	Gastrointestinal disorders (3)	Nausea	Definitely
		Flatulence	Probably
		Loose stools	Definitely
	Nervous system disorders (1)	Bruxism	Probably
	Psychiatric disorders (7)	Anxiety	Definitely
		Perceptual distortion: auditory	Definitely
		Perceptual distortion: visual	Definitely
		Perceptual distortion: self	Definitely
		Sedation	Probably
		Insomnia	Definitely
		Anxiety	Possibly
	Vascular disorders (1)	Blood pressure increased	Definitely
S3	Cardiac disorders (2)	Blood pressure increased	Definitely
		Heart palpitations	Probably
	Nervous system disorders (3)	Restlessness	Definitely
		Dry mouth	Definitely
		Yawning	Definitely
	Psychiatric disorders (5)	Anxiety	Definitely
		Perceptual distortion: visual	Definitely
		Perceptual distortion: temperature	Definitely
		Somnolence	Probably
		Tearfulness	Definitely

“Boccelli sounded ... just divine ... and I was just really on a high with the music, and it was just really intense, positive, and very emotional too in fact ... some sadness but a lot of joy, and it was just very nice”

Discussion

- Our preliminary findings suggest that psilocybin is well-tolerated in cognitively normal older adults.
- Reported AE’s include perceptual, psychological, neurologic, gastrointestinal, and autonomic symptoms.
- Target enrollment is 40 subjects, expected by December 2027.

References

- Morrison, J. H., & Baxter, M. G. (2012). The ageing cortical synapse: Hallmarks and implications for cognitive decline. *Nature Reviews Neuroscience*, 13, 240–250.
- Raval, N. R., et al. (2021). A single dose of psilocybin increases synaptic density and decreases 5-HT2A receptor density in the pig brain. *International Journal of Molecular Sciences*, 22, 835.
- Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., Jesse, R., MacLean, K. A., Barrett, F. S., Cosimano, M. P., & Klinedinst, M. A. (2018). Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *Journal of Psychopharmacology*, 32(1), 49–69.
- Bouchet, L., Sager, Z., Yroni, A., Nigam, K. B., Anderson, B. T., Ross, S., Petridis, P. D., & Beaussant, Y. (2024). Older adults in psychedelic-assisted therapy trials: A systematic review. *Journal of Psychopharmacology*, 38(1), 33–48.

Acknowledgements

PLASTICITY is supported by philanthropic funding through the Berkeley Center for the Science of Psychedelics (BCSP).
IMPACT-AD is supported by National Institute on Aging (NIA) grant numbers R25AG076392 and R13AG067696, and the Alzheimer’s Association (grant number SG-20-693744).