

A Multimodal Lifestyle Intervention Attenuates Hippocampal Subregional Atrophy in Early Alzheimer’s Disease: Results from the PREVENTION Trial

Jennifer E. Bramen^{1,2}, Prabha Siddarth^{3,4}, Molly K. Rapozo⁵, John F. Hodes⁴, Aarthi S. Ganapathi⁴, William M. Sparks⁶, Ynez M. Tongson⁵, Andrea M. Torres⁶, Somayeh Meysami¹, Ryan M. Glatt⁵, Karen J. Miller⁵, Shannel H. Elhelou⁵, Richelin V. Dye⁷, Tess Bookheimer⁸, Susan Bookheimer^{3,4}, Verna R. Porter⁸, Claudia L. Wong⁸, Mihae Kim⁸, Gabriel A. Devenyi⁹, Mallar Chakravarty⁹, Cian Monnin⁹, Cyrus A. Raji¹⁰, Leroy Hood^{11,12}, Jared C. Roach¹¹, David A. Merrill^{8,4}.

Introduction

Medical and lifestyle management are increasingly recognized as crucial for Alzheimer’s disease (AD) prevention and treatment. Hippocampal atrophy is a sensitive marker of early AD, with subregion CA1 strongly linked to episodic memory decline, making it a biologically meaningful target for AD intervention.

Objectives

This 12-month randomized controlled trial tested the overarching hypothesis that a multimodal lifestyle intervention would attenuate hippocampal atrophy, especially in CA1, in patients with early AD and confirmed amyloidosis. Specifically, we tested the following hypotheses:

Active Arm participants would show less hippocampal atrophy than Control Arm participants. Reduced CA1 atrophy would be associated with better preservation of delayed recall.

Method

- 61 participants with early AD confirmed by amyloid biomarkers (active = 31; control = 30), aged 57–89 years (mean = 73.4 ± 7.2).
- The control arm received medical management and structured precision lifestyle recommendations.
- the active arm additionally received individualized health coaching, cognitively stimulating group exercise classes (FitBrain), and nutritional supplementation.

Method Cont’d

- Hippocampal atrophy was evaluated in 48 participants with complete baseline and one-year MRI using the CoBrALab deformation-based morphometry (DBM) pipeline.
- Delayed recall was assessed using a composite delayed recall z-score from verbal and visual memory measures.
- Group differences were tested using FSL Randomizer with TFCE and permutation-based correction (10,000 permutations), adjusting for age, sex, and education, within a bilateral hippocampal ROI.
- Associations between CA1 deformation and memory change were examined controlling for confounders.

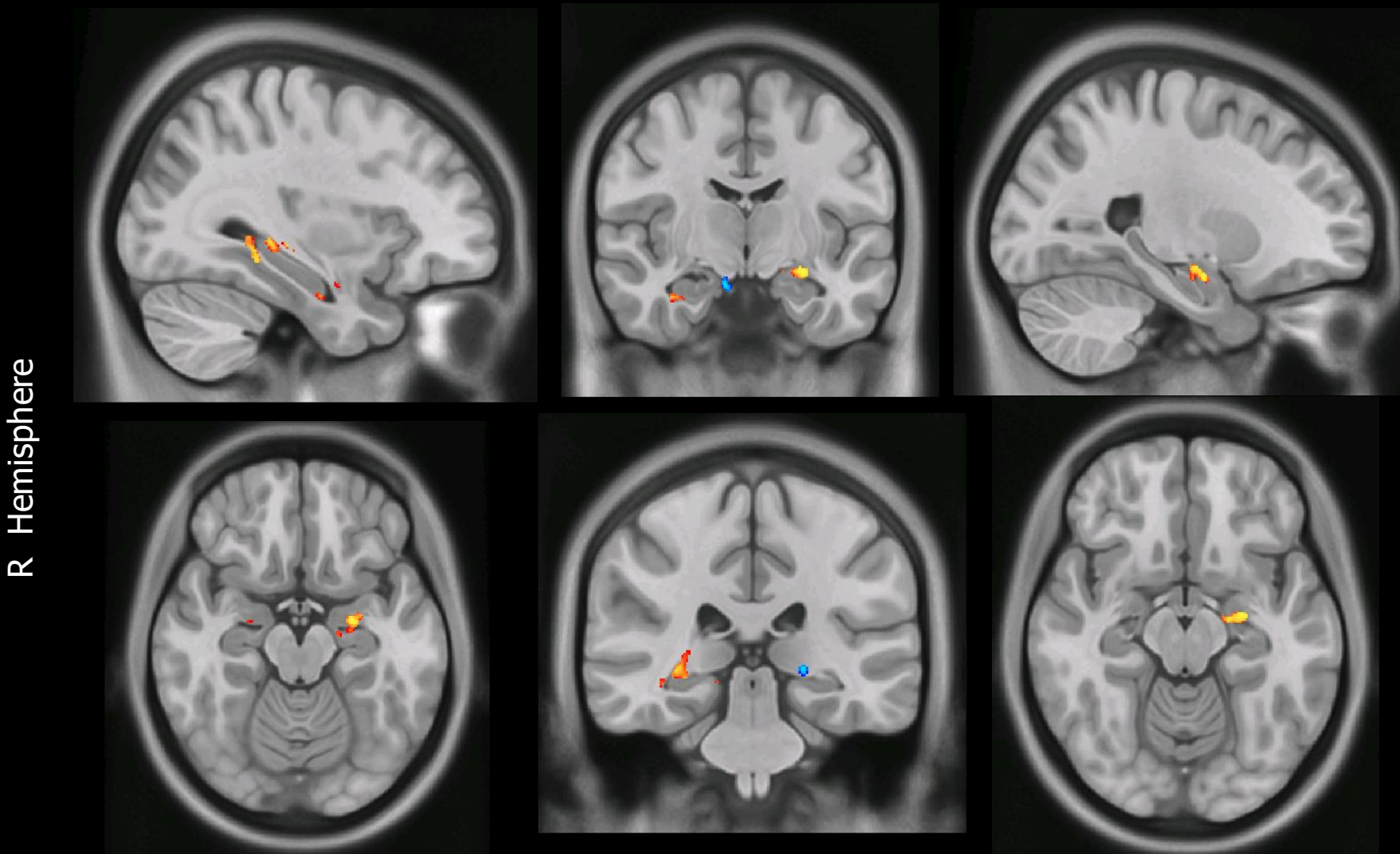
Participants

Table 1. Demographics

	N	Age (±SD, Range) (years)	(% Female)	MoCA (±SD)
Total	61	73.4 (±7.2, 57.0–89.2)	45.9	21.4 (±3.8)
Treatment Arm				
Control	30	74.0 (±7.3, 57.0–89.2)	40.0	22.2 (±3.5)
Active	31	72.8 (±7.2, 59.3–87.0)	51.6	20.7 (±4.0)

Results

Fig. 1A Region-specific differences in hippocampal atrophy between treatment arms.



Differences between arms (active – control) in two-level deformation-based morphometry (DBM) accounting for age, sex, and education was analyzed in N=48 participants. Analyses were restricted to a bilateral hippocampal region of interest defined using the Harvard–Oxford subcortical atlas (≥50% probability). Statistical maps are overlaid on the ICBM MNI 1 mm template. Statistical maps are thresholded using p<0.05, corrected for multiple comparisons using threshold free cluster enhancement (TFCE).

Results Cont’d

Fig. 1B Bar graph demonstrating mean DBM within hippocampal subregion right CA1 in Arm 1 (Control) and Arm 2 (Active)

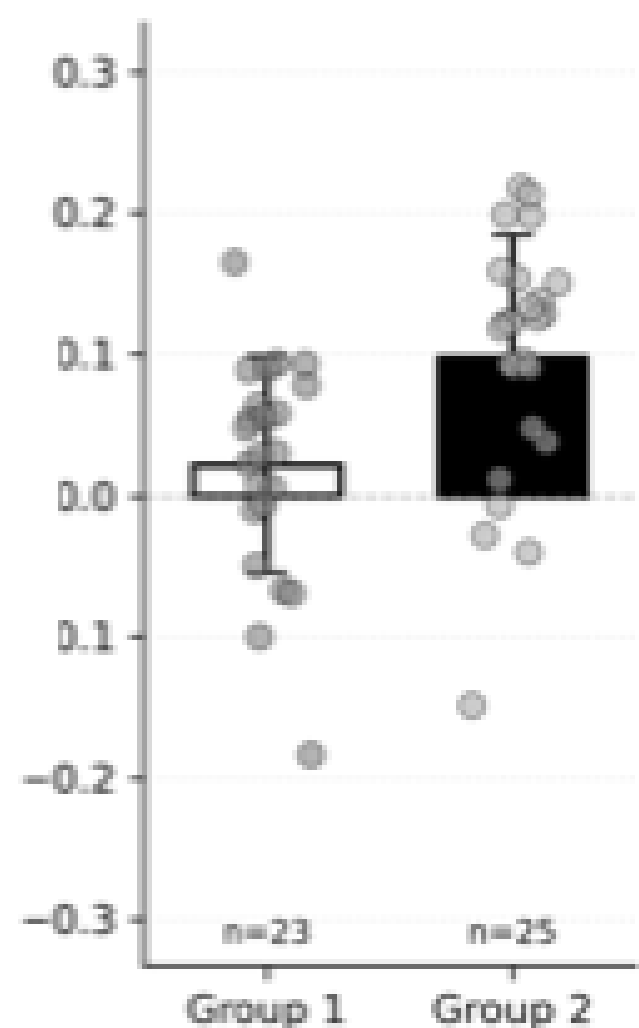
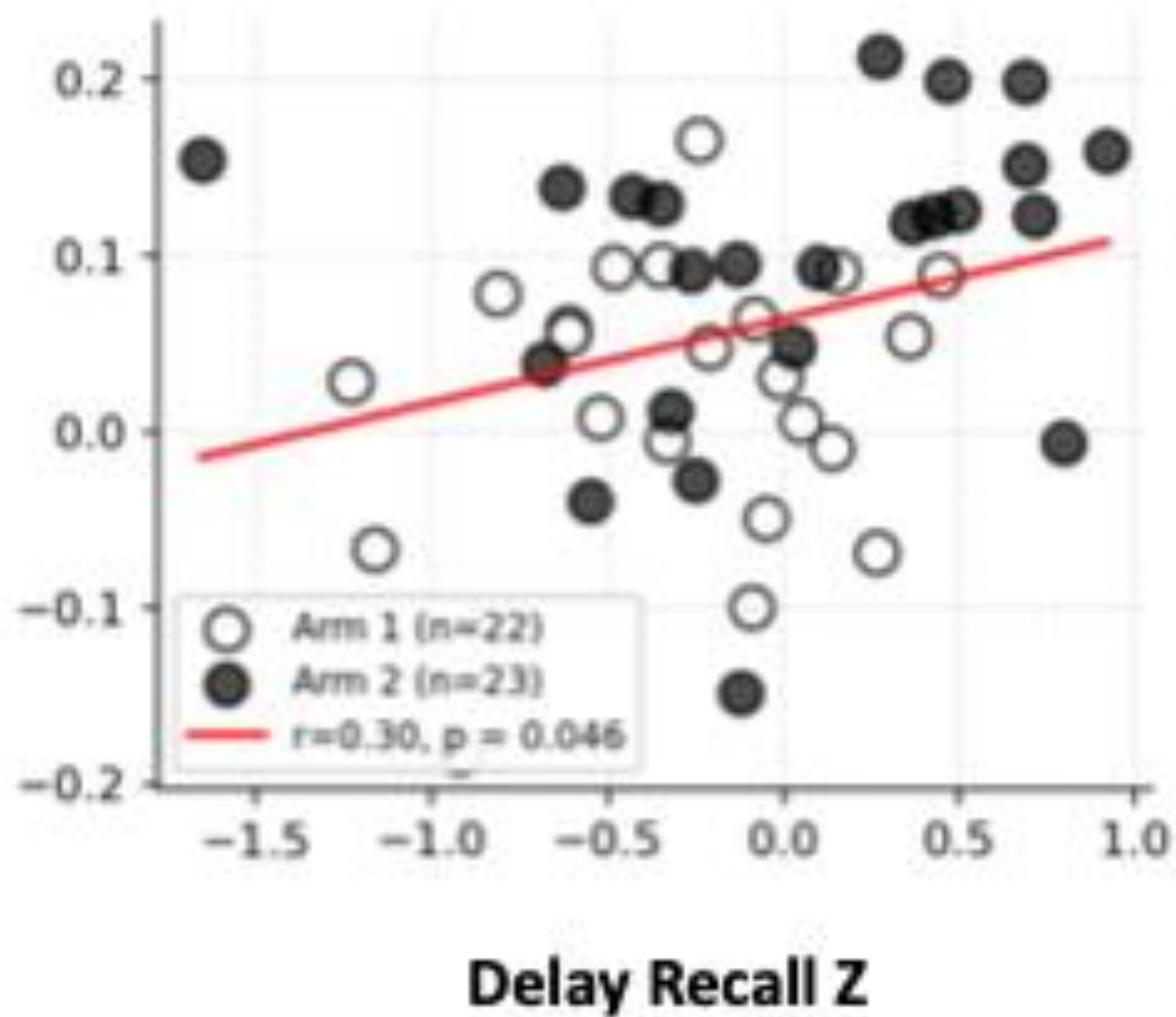


Fig. 1C Line graph demonstrating the correlation between right CA1 and delayed recall.



Results Cont’d

Table 2. Treatment arm differences in hippocampal atrophy measures with two-level deformation-based morphometry

Sub-Region	Right Hemisphere					Left Hemisphere				
	x	y	z	p-value	Cohen's d	x	y	z	p-value	Cohen's d
Anterior body (CA1)	34	-11	-25	0.017*	0.914	-21	-7	-27	0.112†	0.354
DG/CA2/3/4	25	-15	-21	0.427†	-0.030	-28	-13	-20	0.078†	0.465
Fimbria	28	-26	-9	0.033*	0.691	-28	-34	-2	0.393†	-0.092
HATA	16	-10	-17	0.044†	0.988	-20	-12	-14	0.005*	0.924
Posterior tail	32	-32	-3	0.006*	0.962	-36	-31	-10	0.135†	0.288
Subiculum	13	-38	-2	0.013*	0.865	-23	-32	-3	0.009**	-0.847

Differences between arms (active – control) in two-level deformation-based morphometry (DBM) accounting for age, sex, and education was analyzed in N=48 participants. Analyses were restricted to a bilateral hippocampal region of interest defined using the Harvard–Oxford subcortical atlas (≥50% probability). Positive p-values indicate active > control arm. Negative p-values indicated control > active arm. Coordinates are given in Montreal Neurological Institute (MNI) system. Subregional designations are approximate. Due to difficulty in reliably distinguishing subregions at this resolution, we grouped the internal hippocampal fields as Dentate Gyrus/CA2/CA3/CA4 together. Significant clusters that were entirely within cerebrospinal fluid, the parahippocampal gyrus, or the amygdala were not tabulated. Abbreviations: DG, dentate gyrus; HATA, Hippocampal Amygdala Transition Area; Size, cluster extent in mm³. *Denotes statistical significance using p<0.05, corrected for multiple comparisons using threshold free cluster enhancement (TFCE). † Indicates non-significant, uncorrected p-value. ‡ Signifies significance in the control > active arm direction.

Conclusion

A multimodal lifestyle intervention delivered in a clinical setting attenuated hippocampal atrophy in cognitively impaired patients with confirmed amyloidosis. Coupled with the positive association between CA1 change and delayed recall, these findings suggest potential clinical relevance.