SUPPLEMENTARY FIGURES

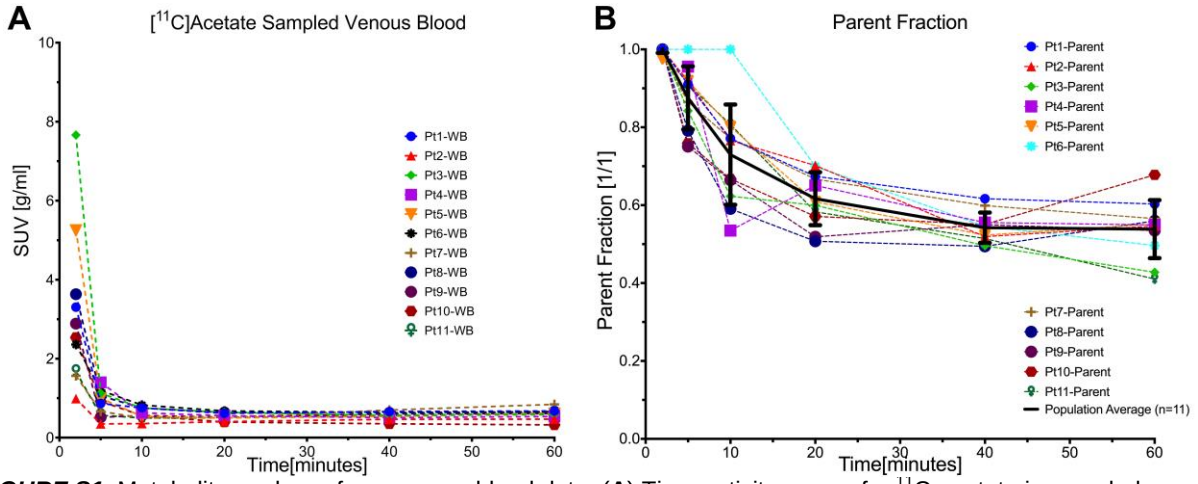

FIGURE S1. Metabolite analyses from venous blood data. (**A**) Time-activity curves for ^{11}C-acetate in sampled venous blood in each participant for 60 minutes. (**B**) Parent compound fraction curves for each participant and the population average (n = 11) over time are shown, where parent fraction = [^{11}C-acetate] / ([^{11}C-acetate] + [^{11}C-CO_2]).

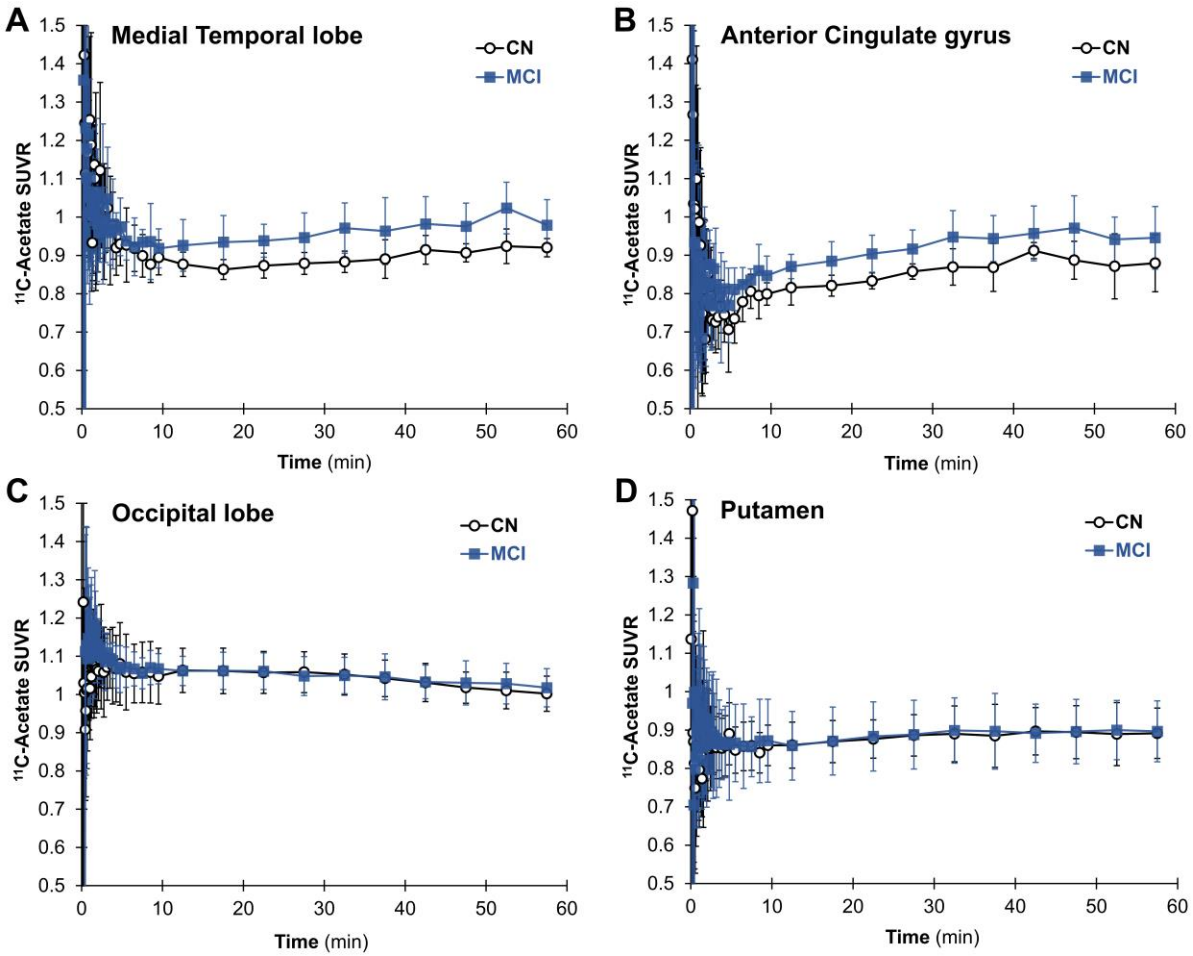

FIGURE S2. Time-activity SUVR curves for ^{11}C-acetate using cerebellar reference for MCI participants and cognitively normal (CN) participants in the (**A**) medial temporal lobe (MTL, which includes the hippocampus) and (**B**)

anterior cingulate gyrus show some between-group differences in ^{11}C-acetate SUVR. Curves from (**C**) occipital lobe and (**D**) putamen do not show major group differences. Error bars represent 1 standard deviation.

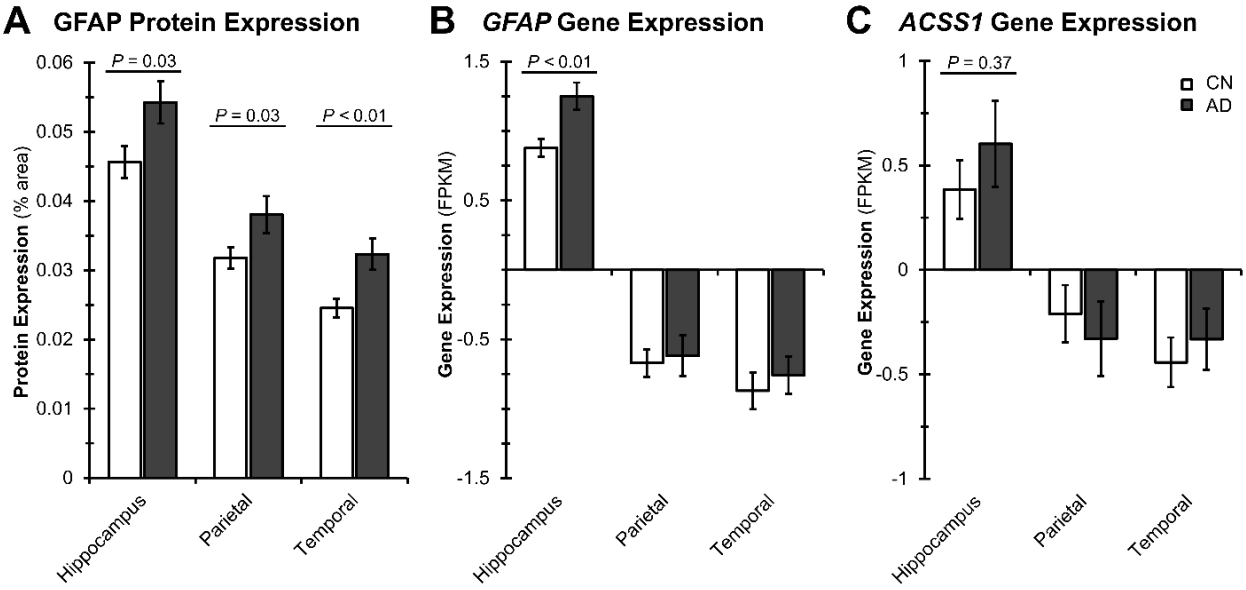

FIGURE S3. Astrocyte markers are elevated in hippocampus of AD brains (n = 25) compared to cognitively normal (CN) brains (n = 50) from (**A**) immunohistochemistry of astrocyte marker glial fibrillary acidic protein (GFAP) (*P* = 0.03) and gene expression (fragments per kilobase of exon per million, FPKM) of astrocyte-associated genes (**B**) *GFAP* (*P* = 0.01) and (**C**) *ACSS1* (*P* = 0.37). Bar plots denote mean and standard error of the mean. *P* values from 2-sample independent *t*-tests shown. See Supplemental Methods for additional information.

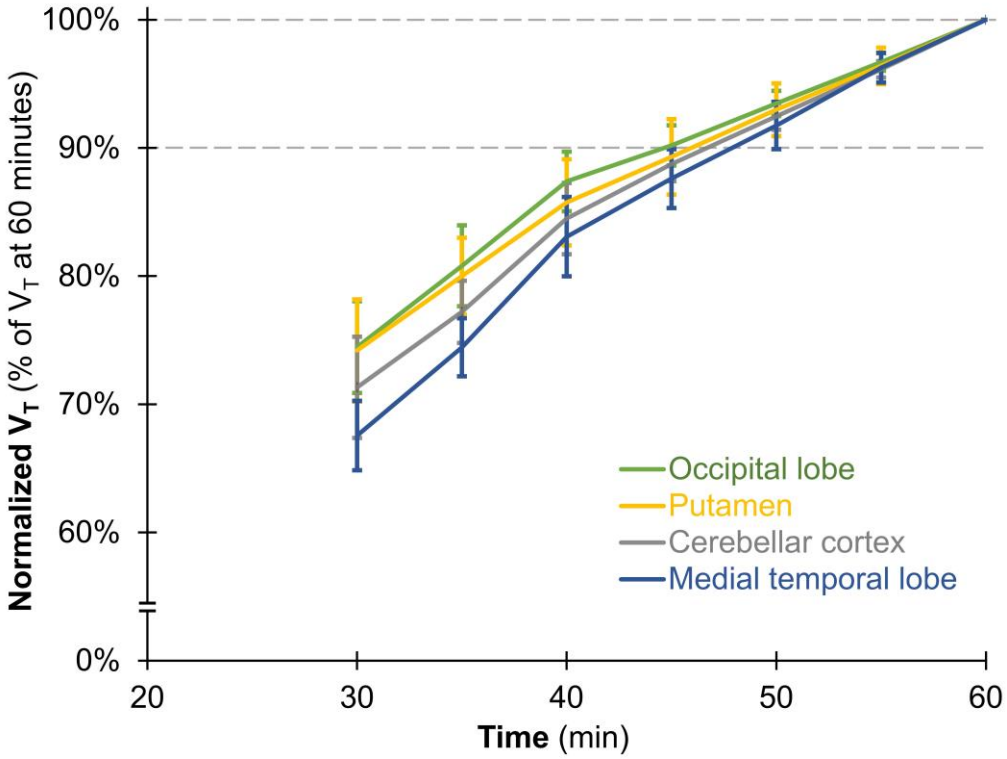

FIGURE S4. Time stability analysis of ^{11}C-acetate distribution volumes (V_T) in 4 brain regions, including the occipital lobe, putamen, cerebellar cortex and medial temporal lobe. Averages and standard deviation of V_T values are shown. Distribution volumes across regions are relatively stable at the range of 40 to 60 minutes post injection.

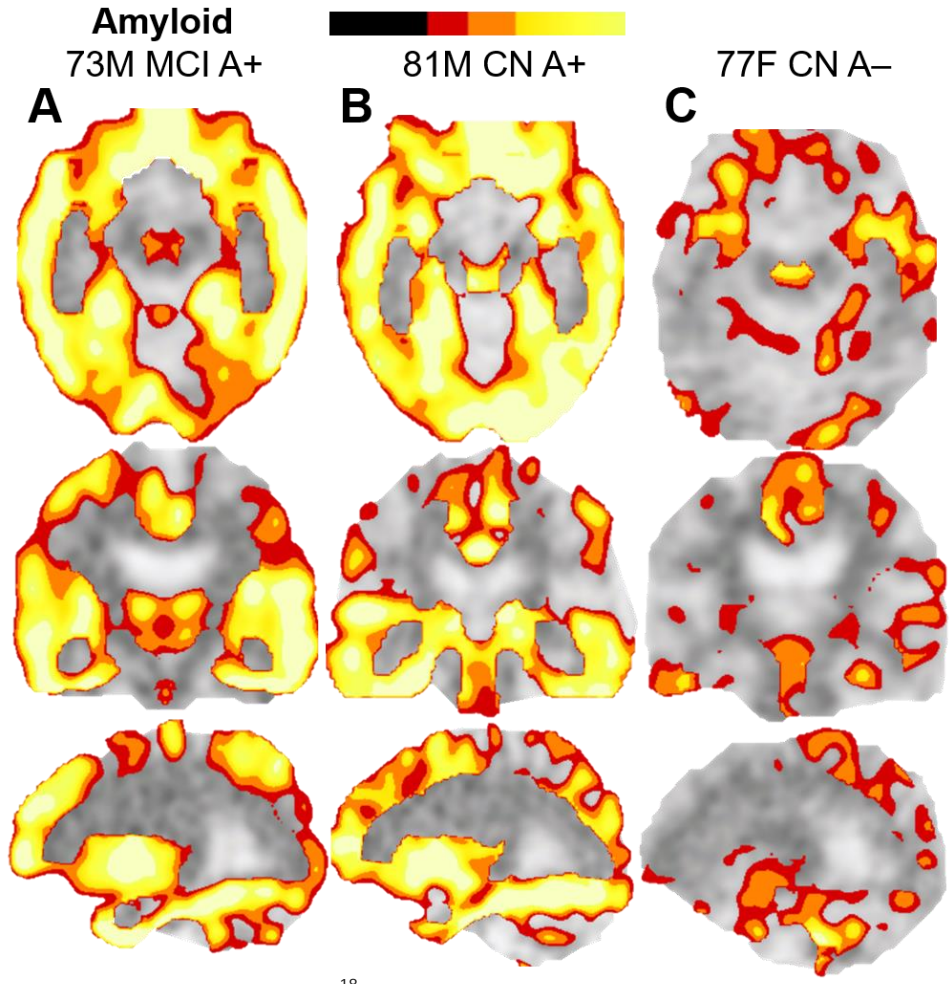

FIGURE S5. Examples of z-score maps of ^{18}F-florbetaben (amyloid) PET in representative amyloid-positive (A+) participants with (**A**) mild cognitive impairment (MCI) or (**B**) normal cognition (CN) compared to (**C**) amyloid-negative (A–) cognitively normal controls. The participants in Figure S5A and S5B are the same as in Figure 1A and 1B, respectively. Figure S5C shows an A– cognitively normal adult. Data visualization was performed on MIM.

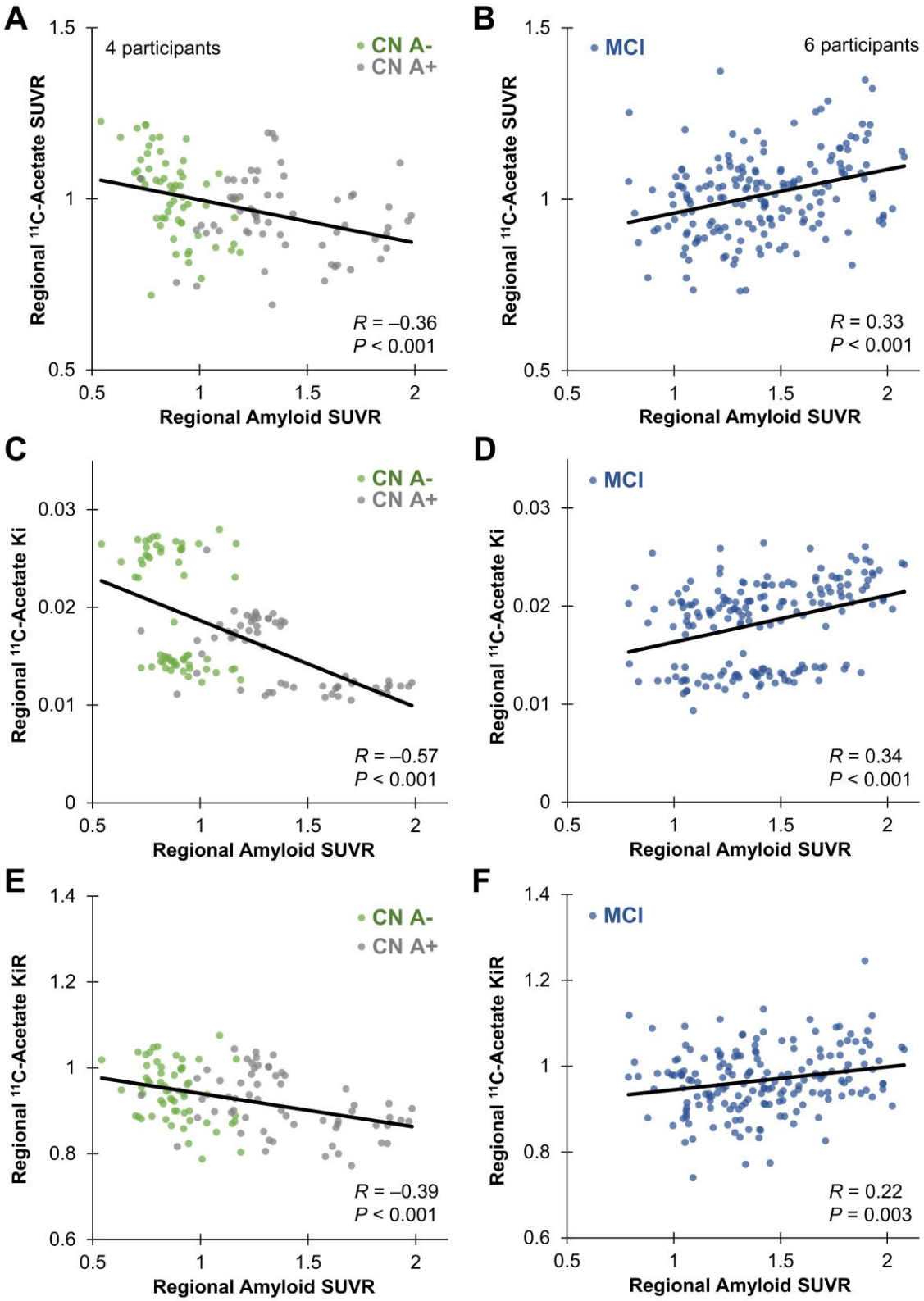

FIGURE S6. Plots of regional ^{11}C-acetate vs. ^{18}F-florbetaben amyloid SUVR in (**A**) 4 CN participants (amyloid-negative, green; amyloid-positive, gray) and (**B**) 6 participants with MCI (blue). Plots of regional ^{11}C-acetate Ki flux vs. amyloid SUVR in (**C**) CN and (**D**) MCI. Plots of regional ^{11}C-acetate flux ratio vs. amyloid SUVR in (**E**) CN and (**F**)

MCI. Each point represents 1 region in 1 participant. There are 30 regions and 10 participants with both ^{11}C-acetate and ^{18}F-florbetaben scans. Linear mixed-effects model correlations and *P* values are shown.

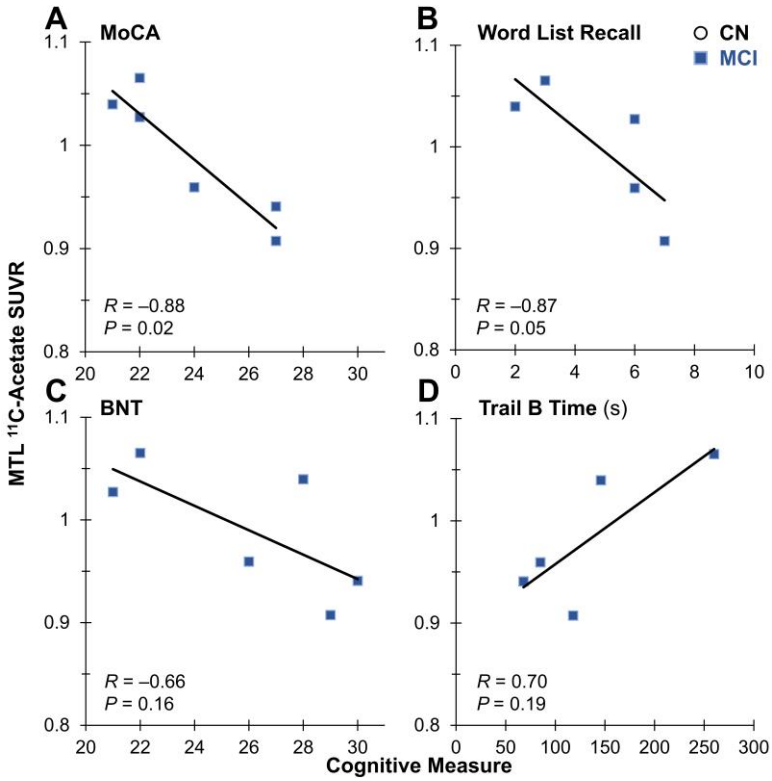

FIGURE S7. MTL ^{11}C-acetate retention in MCI participants only displays significant correlations with (**A**) Montreal Cognitive Assessment (MoCA) and (**B**) Word List Recall memory. Relationship trends with (**C**) Boston Naming Test (BNT) and (**D**)Trail B Time (s) are also shown. Regressions, Spearman correlations and *P* values shown.

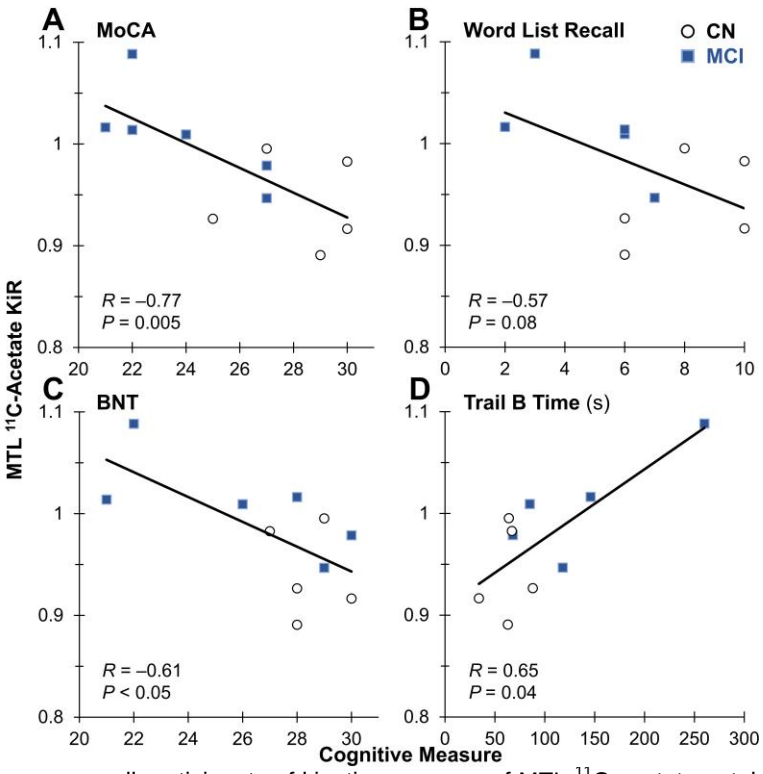

FIGURE S8. Comparison across all participants of kinetic measures of MTL ^{11}C-acetate uptake vs. cognitive tests of (**A**) Montreal Cognitive Assessment (MoCA), (**B**) Word List Recall, (**C**) Boston Naming Test (BNT) and (**D**) Trail B Time (s). Linear regressions, Spearman correlations and *P* values are shown.

TABLE S1. ^{11}C-Acetate retention (in SUVR) in limbic regions, with means and standard deviation in parentheses. *P* < 0.05 in bold.

Limbic Regions	Cognitively Normal	MCI	Cohen *d*	*P* Value
Primary region				
Medial temporal lobe	0.91 (0.02)	0.99 (0.06)	1.76	**0.03**
Exploratory regions				
Cingulate gyrus, Anterior	0.89 (0.06)	0.95 (0.06)	1.15	0.10
Cingulate gyrus, Middle	0.98 (0.05)	1.05 (0.05)	1.24	0.09
Cingulate gyrus, Posterior	1.00 (0.09)	1.04 (0.06)	0.55	0.40
Fusiform gyrus	0.97 (0.08)	1.04 (0.07)	0.90	0.18

TABLE S2. ^{11}C-Acetate Patlak kinetic flux ratio (KiR) in limbic regions with means and standard deviation (in parentheses). *P* < 0.05 in bold.

Limbic Regions	Cognitively Normal	MCI	Cohen *d*	*P* value
Primary regions				
Medial temporal lobe	0.94 (0.04)	1.01 (0.05)	1.55	**0.04**
Exploratory regions				
Cingulate gyrus, Anterior	0.91 (0.10)	0.97 (0.06)	0.92	0.25
Cingulate gyrus, Middle	0.94 (0.07)	0.98 (0.05)	0.66	0.36
Cingulate gyrus, Posterior	0.92 (0.06)	0.95 (0.06)	0.50	0.33
Fusiform gyrus	0.96 (0.08)	1.05 (0.05)	1.35	**0.04**

SUPPLEMENTARY METHODS

Ex vivo Biomarker Expression Analysis

Expression analysis of astrocyte marker genes and proteins was performed using publicly available data from the Allen Brain Atlas Adult Changes in Thought study (http://aging.brain-map.org/) [1]. The study has gene expression profiles in 3 cortical ROIs for 56 participants with normal cognition and 30 participants with AD. Hypothesis-driven biomarker measurements were performed with astrocyte marker genes associated with astrocyte activation: glial fibrillary acidic protein (*GFAP*), a structural protein specific to astrocytes, and acetyl-CoA synthetase I (*ACSS1*), a metabolic enzyme enriched in astrocytes that bioactivates acetate [2].

Supplementary References

1. J. A. Miller, A. Guillozet-Bongaarts, L. E. Gibbons, et al., “Neuropathological and transcriptomic characteristics of the aged brain,” *Elife*, vol. 6, article e31126, 2017.
2. M. J. Simon, M. X. Wang, et al., “Transcriptional network analysis of human astrocytic endfoot genes reveals region-specific associations with dementia status and tau pathology,” *Sci Rep*, vol 8, no. 1, article 12389, 2018.