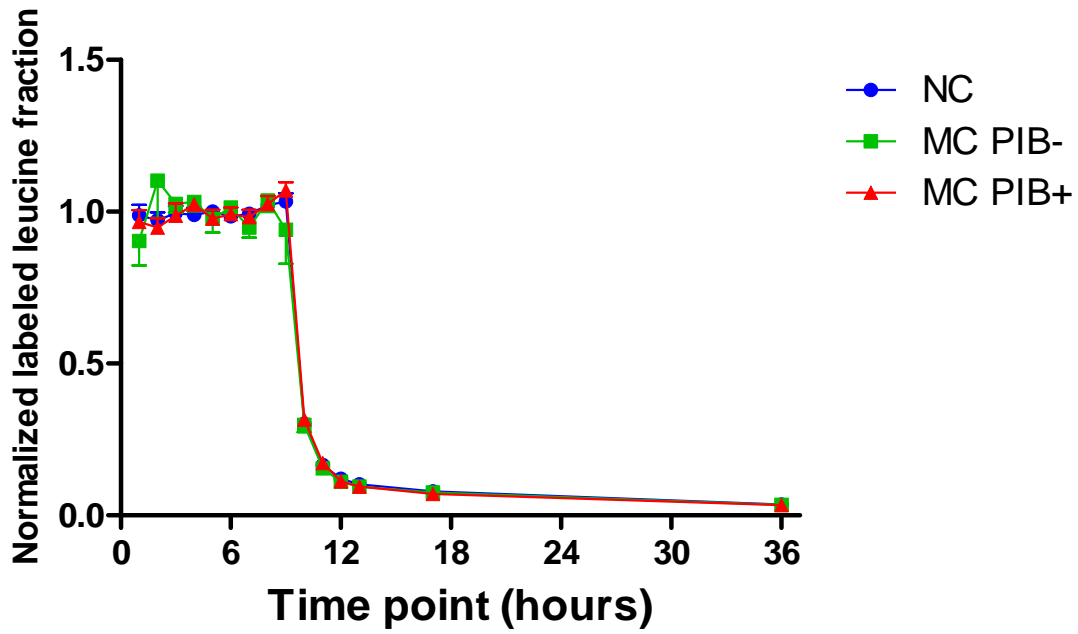


Fig. S1. Time course of plasma leucine isotopic enrichment

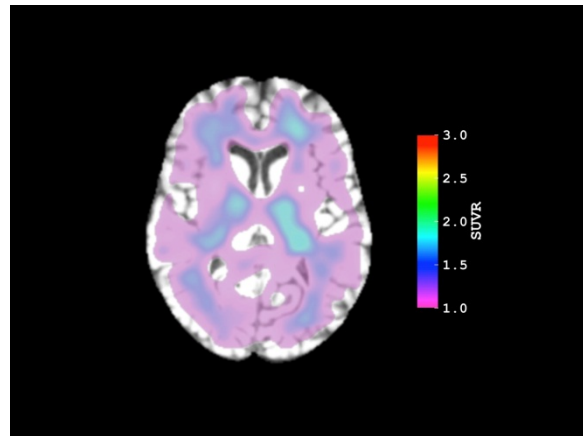
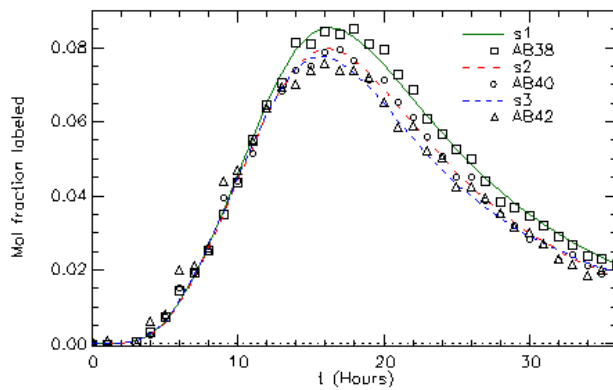


Plasma leucine enrichment was normalized to the enrichment plateau, and compared by mutation status (NC = non-mutation carriers; MC = mutation carriers) and amyloid deposition (PIB- or PIB+). Error bars represent SEM.

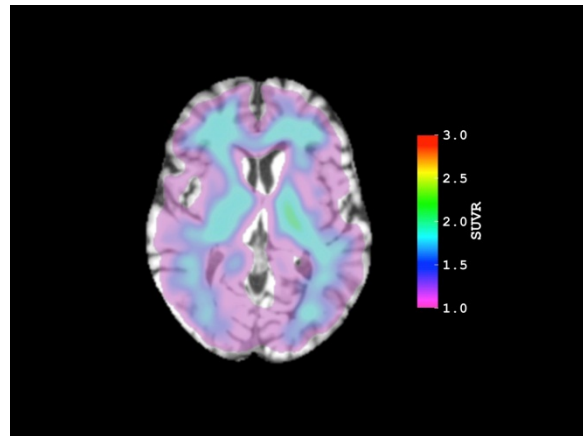
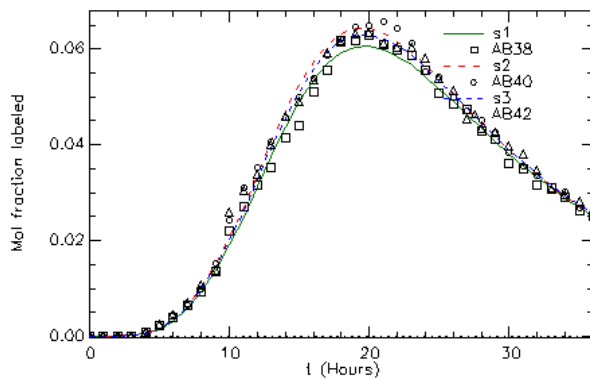
Fig. S4. Isotopic enrichment time courses of CSF A β peptides in individual non-mutation carrier subjects

The PIB mean cortical binding potential score, the ratio of A β 42:A β 40 total fractional turnover rates (FTR), the ratio of CSF A β 42:A β 40 concentrations, and the presence or absence of the exchange process for A β 42 revealed by the model are also tabulated for each participant. Summary values of these measures are tabulated after the last participant within the group. The isotopic enrichment time courses of A β 38 (squares, solid green line), 40 (circles, dashed red line), and 42 (triangles, dashed blue line) are presented for each participant. Lines represent model fits to each participant's data. An image with PET-PIB labeling superimposed over MRI is also shown for each participant. PIB images are displayed as Standardized Uptake Value Ratios (SUVRs) with the cerebellar gray matter used as the reference tissue.

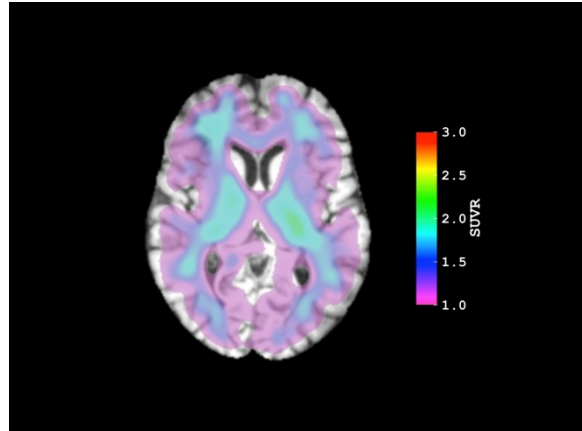
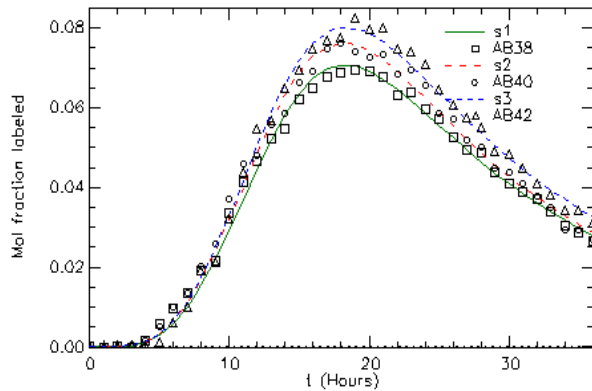
PIB MCBP score= 0.026
 A β 42:A β 40 FTR ratio: 1.06
 CSF [A β 42]:[A β 40] ratio: 0.129
 Exchange of A β 42: Yes



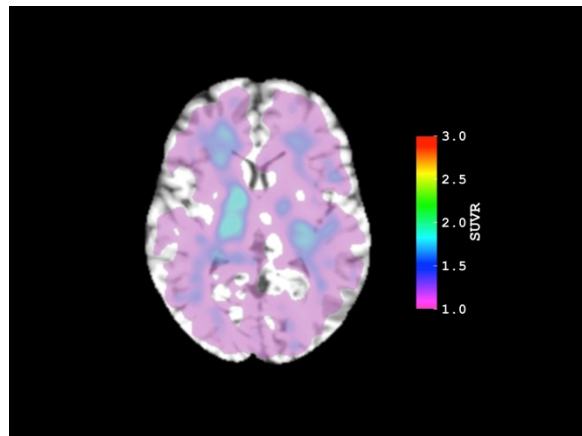
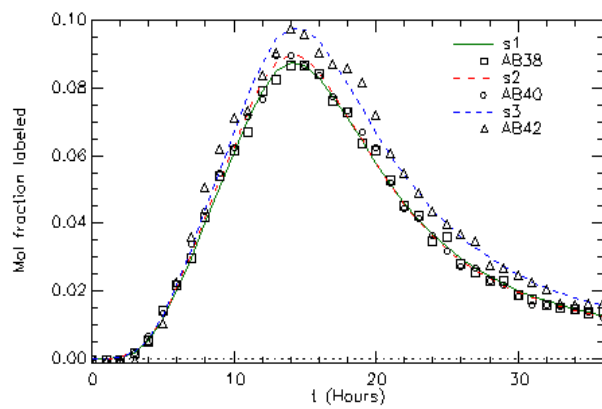
PIB MCBP score = 0.051
 A β 42:A β 40 FTR ratio: 0.966
 CSF [A β 42]:[A β 40] ratio: 0.153
 Exchange of A β 42: No



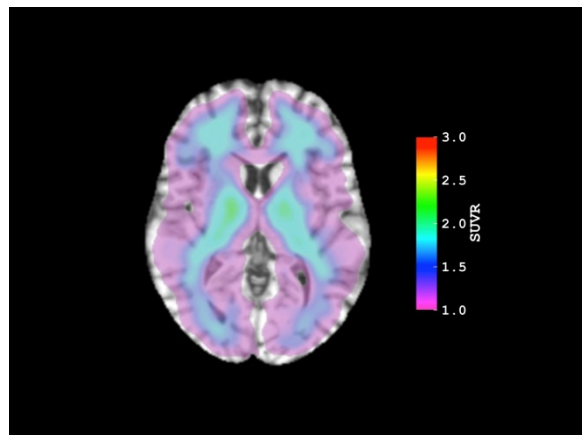
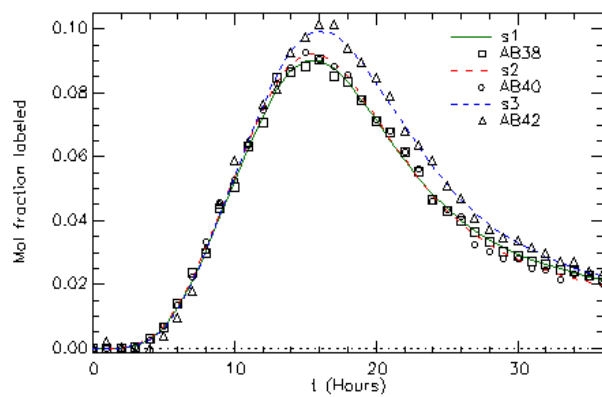
PIB MCBP score = -0.013
A β 42:A β 40 FTR ratio: 0.930
CSF [A β 42]:[A β 40] ratio: 0.163
Exchange of A β 42: No



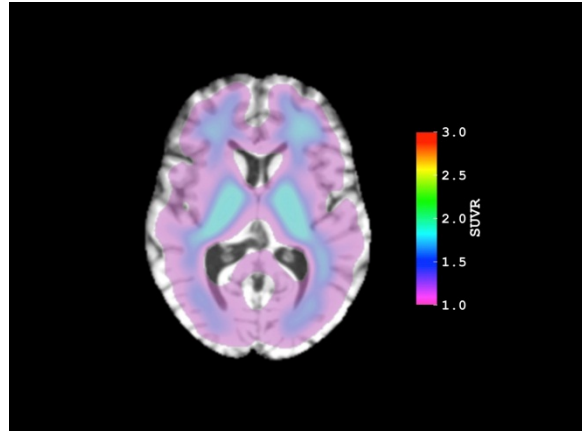
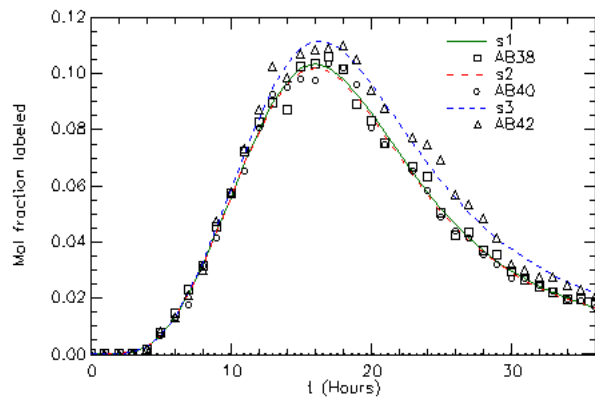
PIB MCBP score = -0.026
A β 42:A β 40 FTR ratio: 0.889
CSF [A β 42]:[A β 40] ratio: 0.169
Exchange of A β 42: No



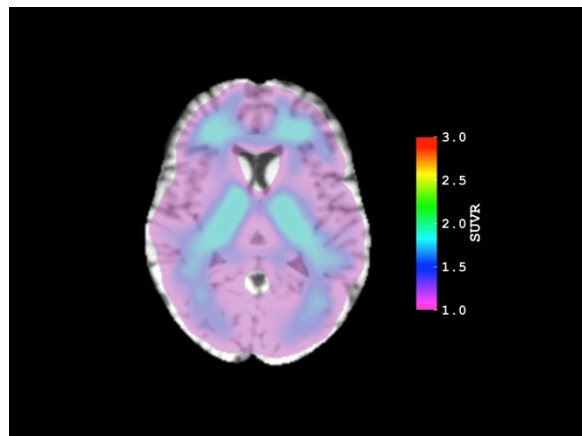
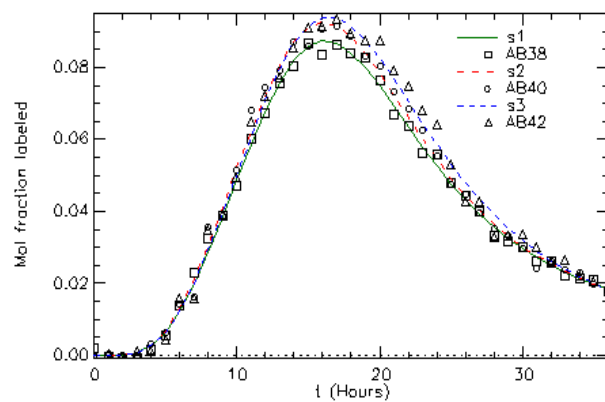
PIB MCBP score = -0.025
A β 42:A β 40 FTR ratio: 0.781
CSF [A β 42]:[A β 40] ratio: 0.159
Exchange of A β 42: Yes



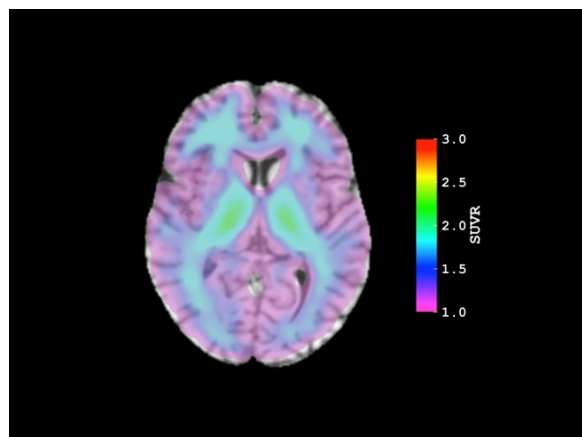
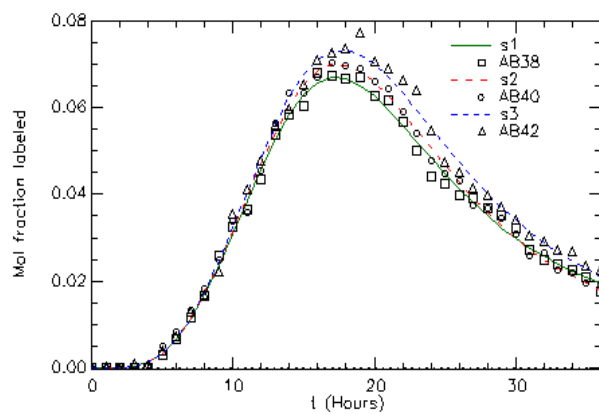
PIB MCBP score = 0.031
A β 42:A β 40 FTR ratio: 0.870
CSF [A β 42]:[A β 40] ratio: 0.155
Exchange of A β 42: No



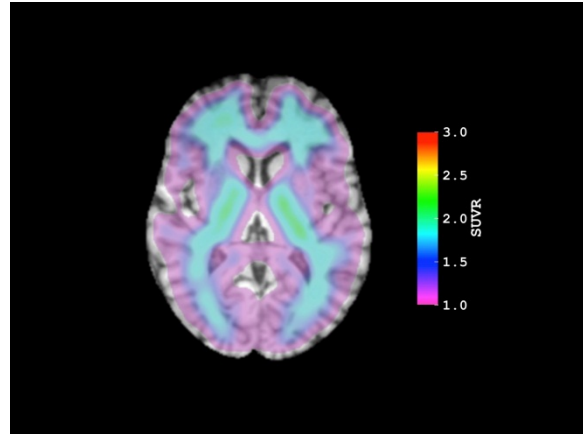
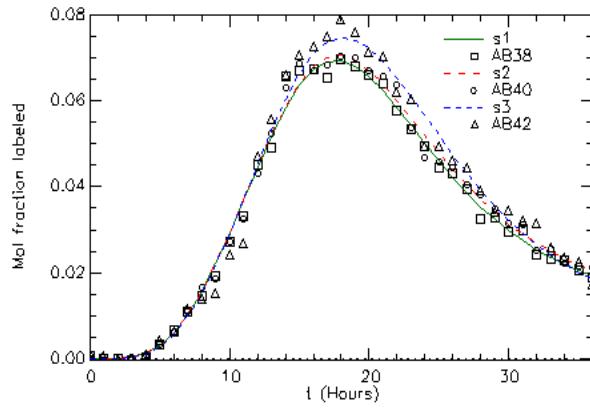
PIB MCBP score = 0.094
A β 42:A β 40 FTR ratio: 0.905
CSF [A β 42]:[A β 40] ratio: 0.138
Exchange of A β 42: No



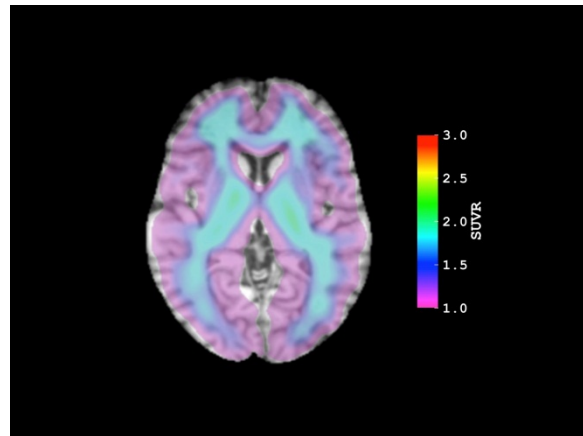
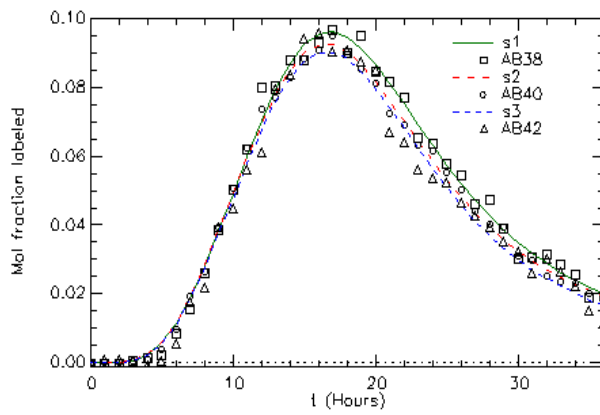
PIB MCBP score = 0.120
A β 42:A β 40 FTR ratio: 0.910
CSF [A β 42]:[A β 40] ratio: 0.155
Exchange of A β 42: No



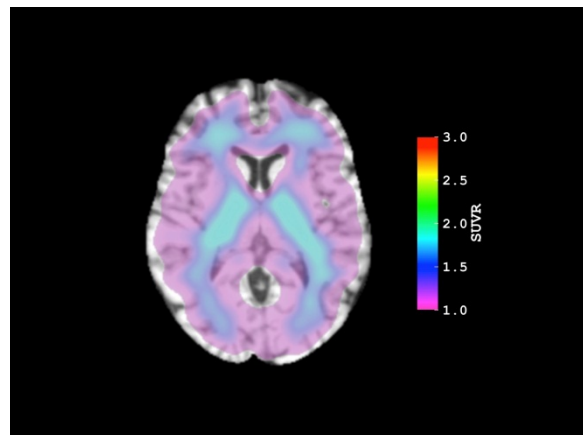
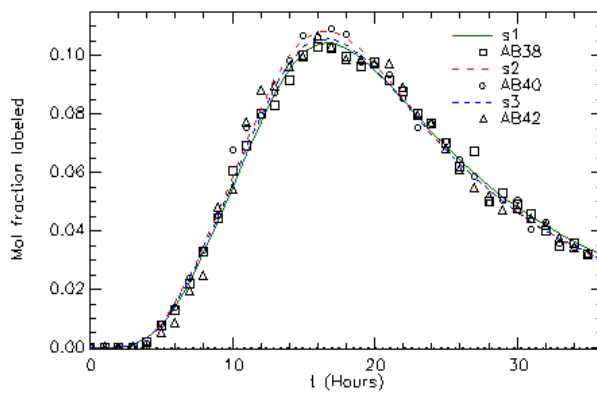
PIB MCBP score = 0.000
 $A\beta_{42}:A\beta_{40}$ FTR ratio: 0.944
CSF $[A\beta_{42}]:[A\beta_{40}]$ ratio: 0.158
Exchange of $A\beta_{42}$: No



PIB MCBP score = 0.016
 $A\beta_{42}:A\beta_{40}$ FTR ratio: 1.022
CSF $[A\beta_{42}]:[A\beta_{40}]$ ratio: 0.147
Exchange of $A\beta_{42}$: No



PIB MCBP score = 0.013
 $A\beta_{42}:A\beta_{40}$ FTR ratio: 0.972
CSF $[A\beta_{42}]:[A\beta_{40}]$ ratio: 0.126
Exchange of $A\beta_{42}$: No

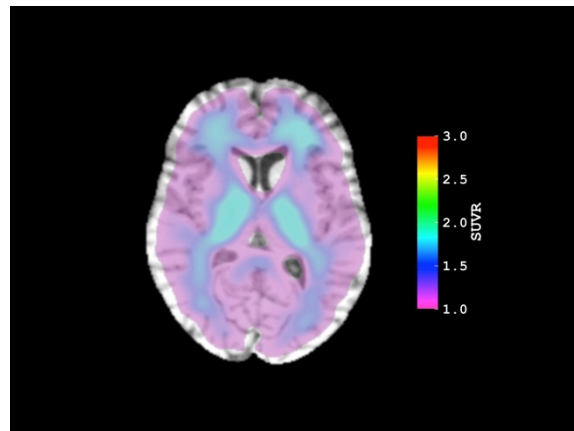
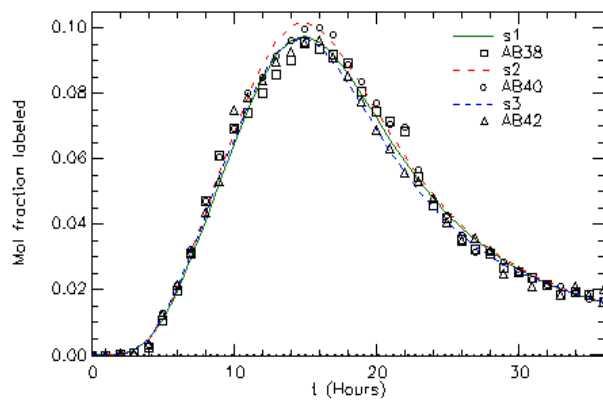


PIB MCBP score = 0.026

A β 42:A β 40 FTR ratio: 1.052

CSF [A β 42]:[A β 40] ratio: 0.139

Exchange of A β 42: Yes



Summary of Non-mutation carrier group

PIB MCBP score: 0.026 ± 0.045

A β 42:A β 40 FTR ratio: 0.942 ± 0.080

CSF [A β 42]:[A β 40] ratio: 0.149 ± 0.135

Exchange of A β 42: 3/12

Fig. S5. Isotopic enrichment time courses of CSF A β peptides in mutation carriers with amyloid plaques (PIB+)

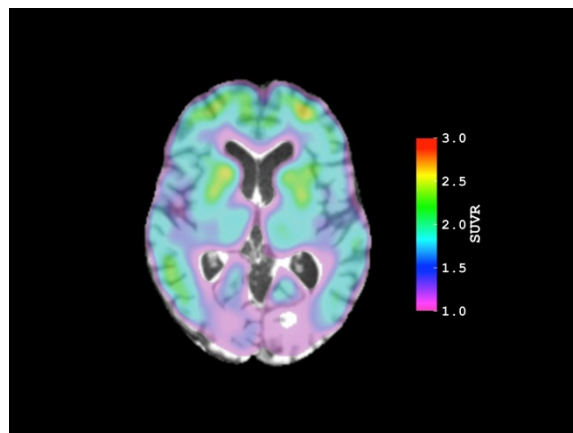
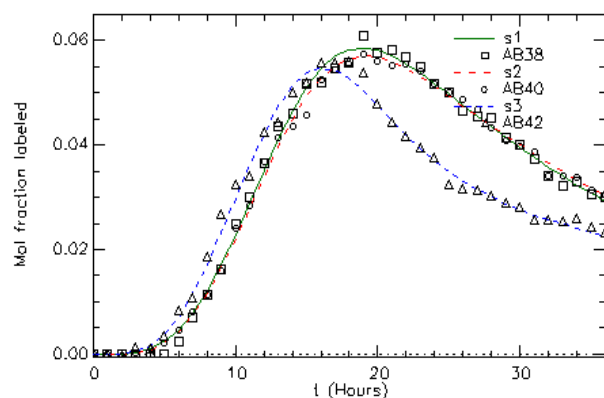
See **Fig. S4** for details.

PIB MCBP score = 0.725

A β 42:A β 40 FTR ratio: 2.04

CSF [A β 42]:[A β 40] ratio: 0.084

Exchange of A β 42: Yes

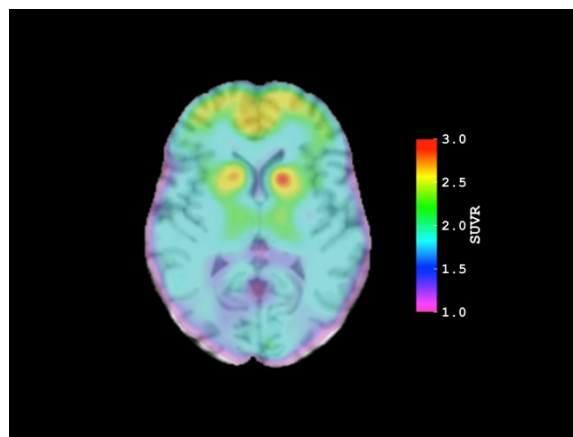
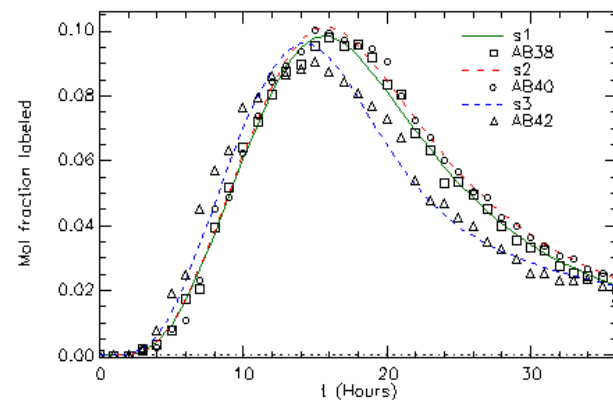


PIB MCBP score = 0.779

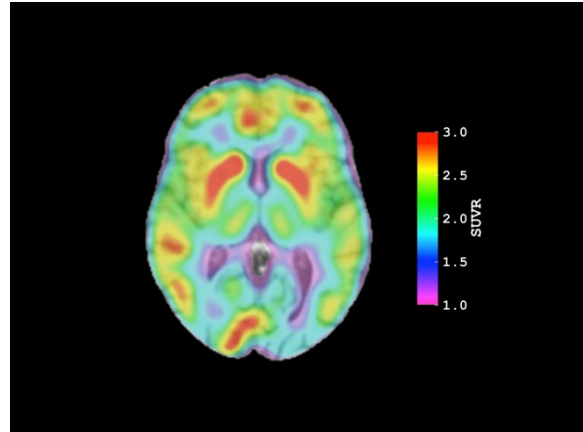
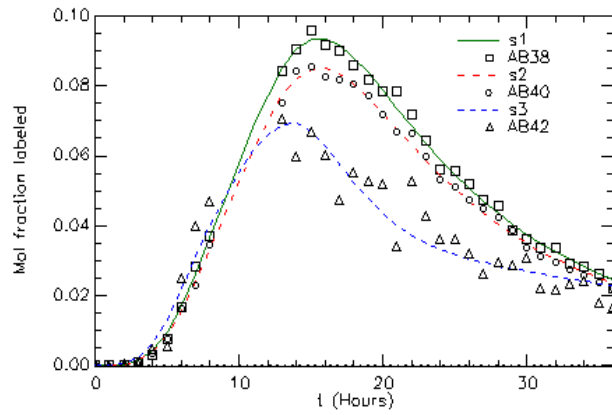
A β 42:A β 40 FTR ratio: 1.70

CSF [A β 42]:[A β 40] ratio: 0.087

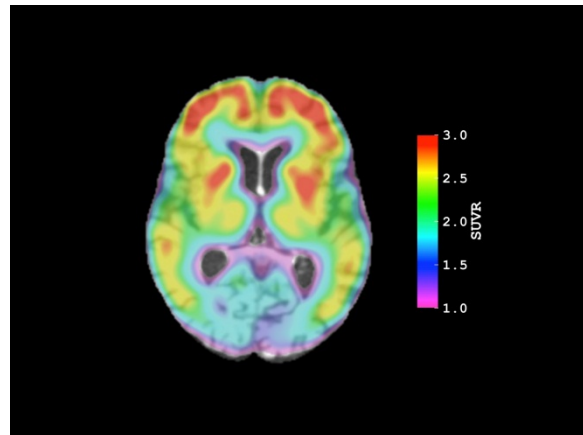
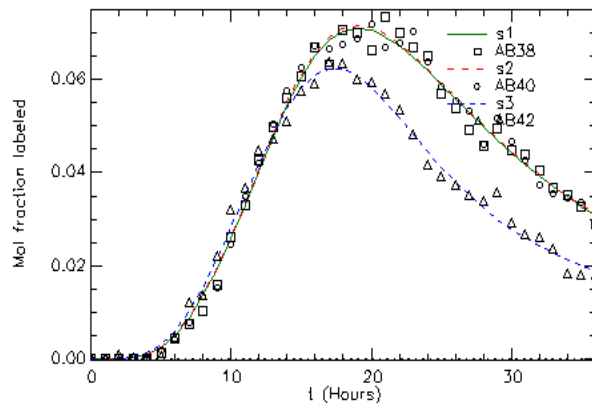
Exchange of A β 42: Yes



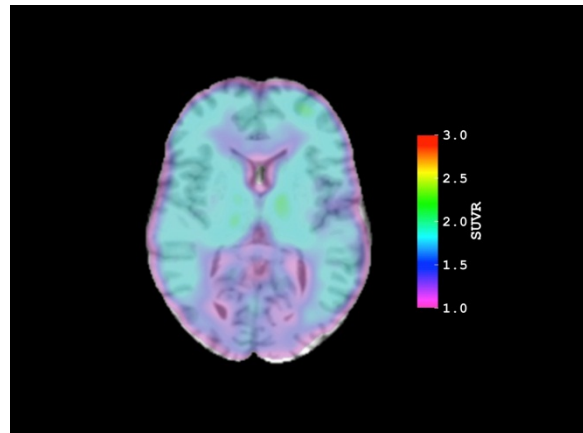
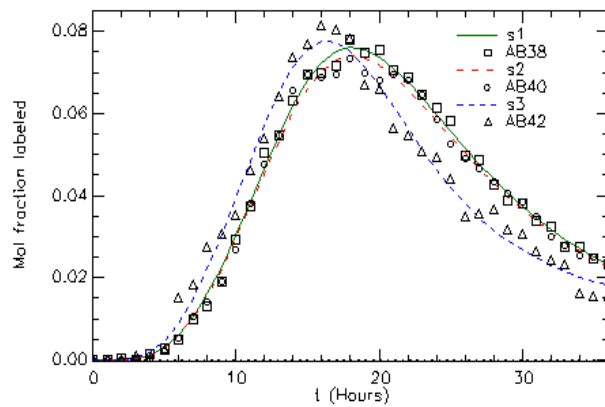
PIB MCBP score = 1.025
 $A\beta_{42}:A\beta_{40}$ FTR ratio: 2.15
CSF $[A\beta_{42}]:[A\beta_{40}]$ ratio: 0.081
Exchange of $A\beta_{42}$: Yes



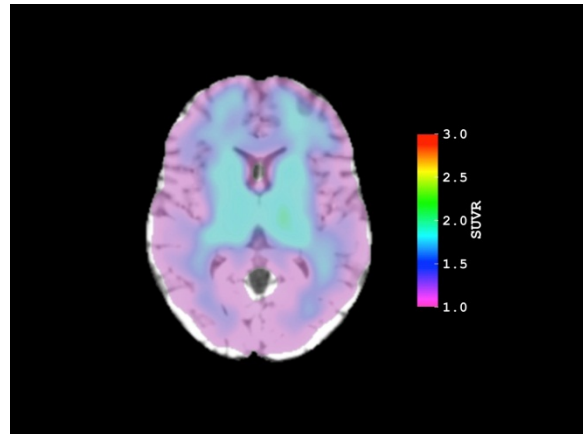
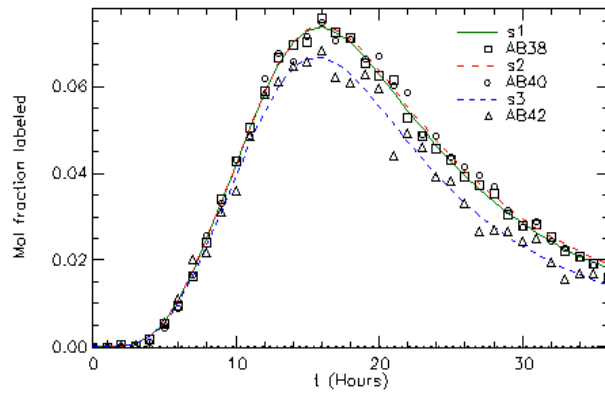
PIB MCBP score = 1.261
 $A\beta_{42}:A\beta_{40}$ FTR ratio: 1.68
CSF $[A\beta_{42}]:[A\beta_{40}]$ ratio: 0.104
Exchange of $A\beta_{42}$: Yes



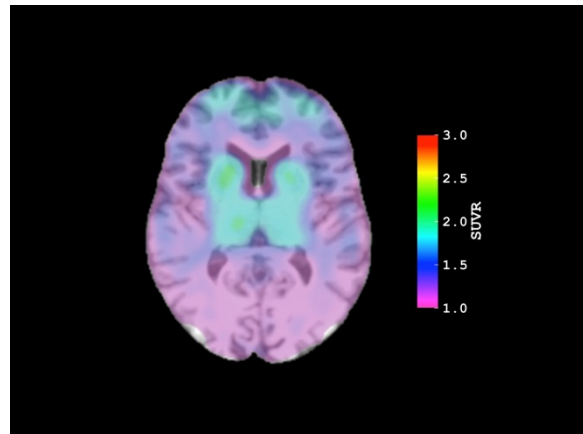
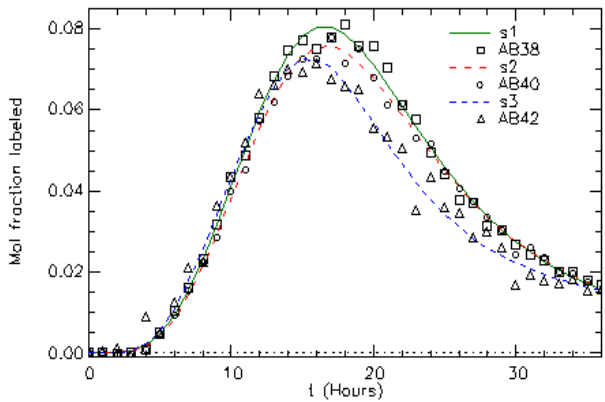
PIB MCBP score = 0.378
 $A\beta_{42}:A\beta_{40}$ FTR ratio: 1.84
CSF $[A\beta_{42}]:[A\beta_{40}]$ ratio: 0.081
Exchange of $A\beta_{42}$: Yes



PIB MCBP score = 0.239
A β 42:A β 40 FTR ratio: 1.14
CSF [A β 42]:[A β 40] ratio: 0.139
Exchange of A β 42: No



PIB MCBP score = 0.373
A β 42:A β 40 FTR ratio: 1.50
CSF [A β 42]:[A β 40] ratio: 0.135
Exchange of A β 42: Yes



Summary of Mutation carrier PIB+ group

PIB MCBP score: 0.683 ± 0.376
A β 42:A β 40 FTR ratio: 1.72 ± 0.336
CSF [A β 42]:[A β 40] ratio: 0.102 ± 0.026
Exchange of A β 42: 6/7

Fig. S6. Isotopic enrichment time courses of CSF A β peptides in mutation carriers without amyloid plaques (PIB-)

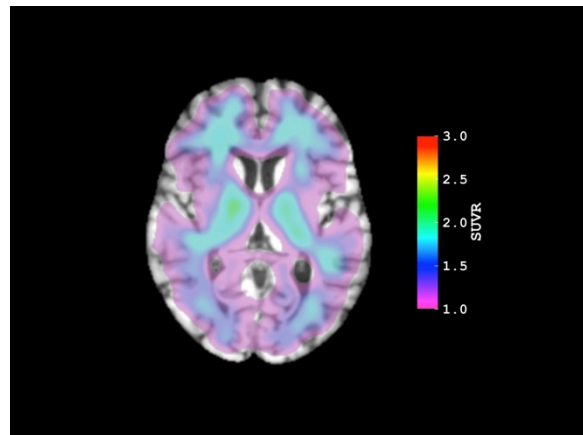
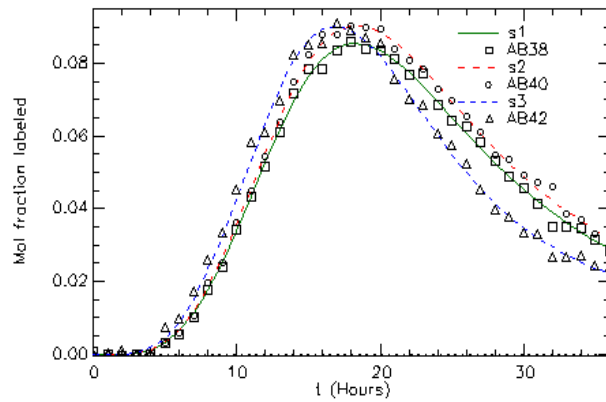
See **Fig. S4** for details.

PIB MCBP score = 0.033

A β 42:A β 40 FTR ratio: 1.62

CSF [A β 42]:[A β 40] ratio: 0.100

Exchange of A β 42: Yes

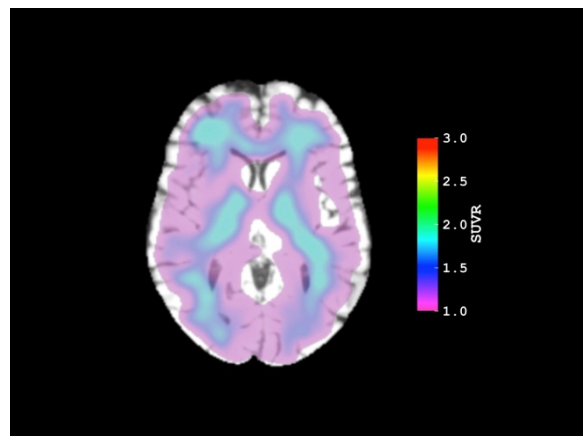
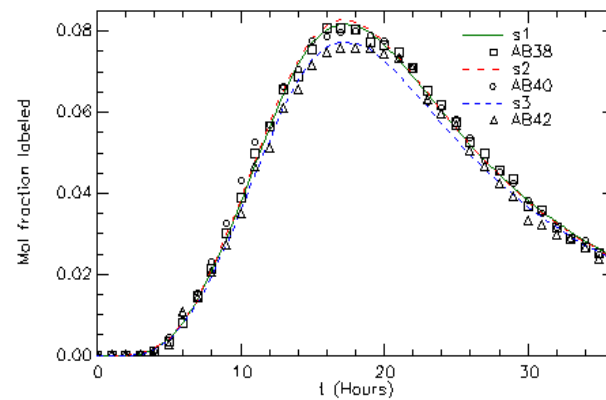


PIB MCBP score = 0.015

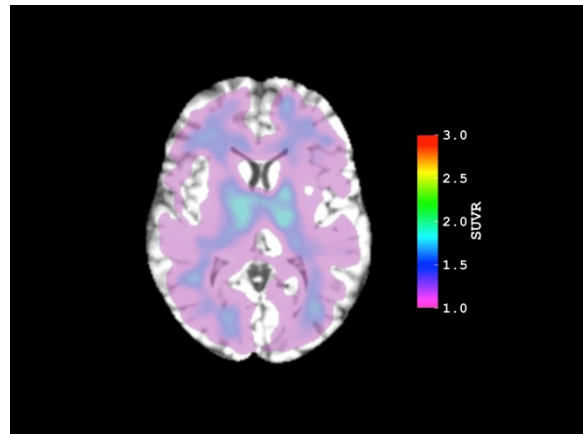
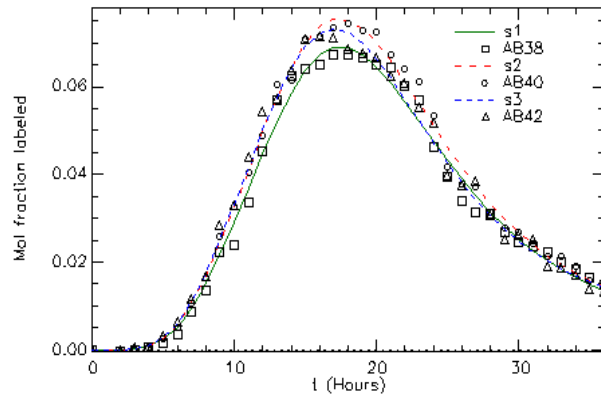
A β 42:A β 40 FTR ratio: 0.967

CSF [A β 42]:[A β 40] ratio: 0.215

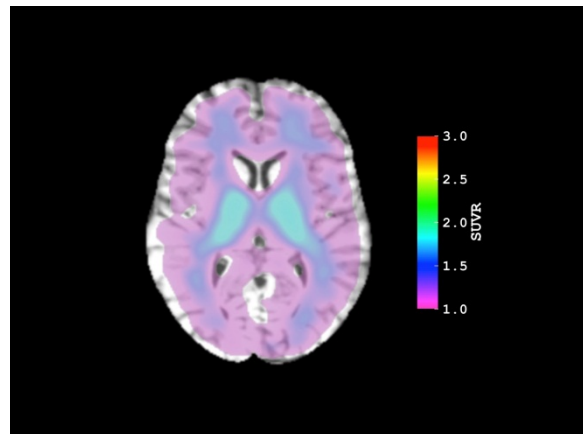
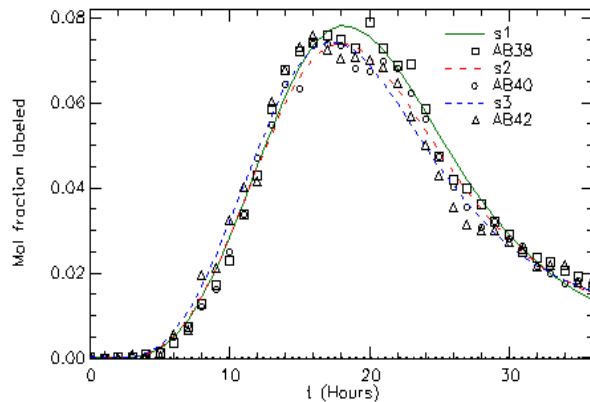
Exchange of A β 42: No



PIB MCBP score = -0.066
A β 42:A β 40 FTR ratio: 1.11
CSF [A β 42]:[A β 40] ratio: 0.161
Exchange of A β 42: Yes



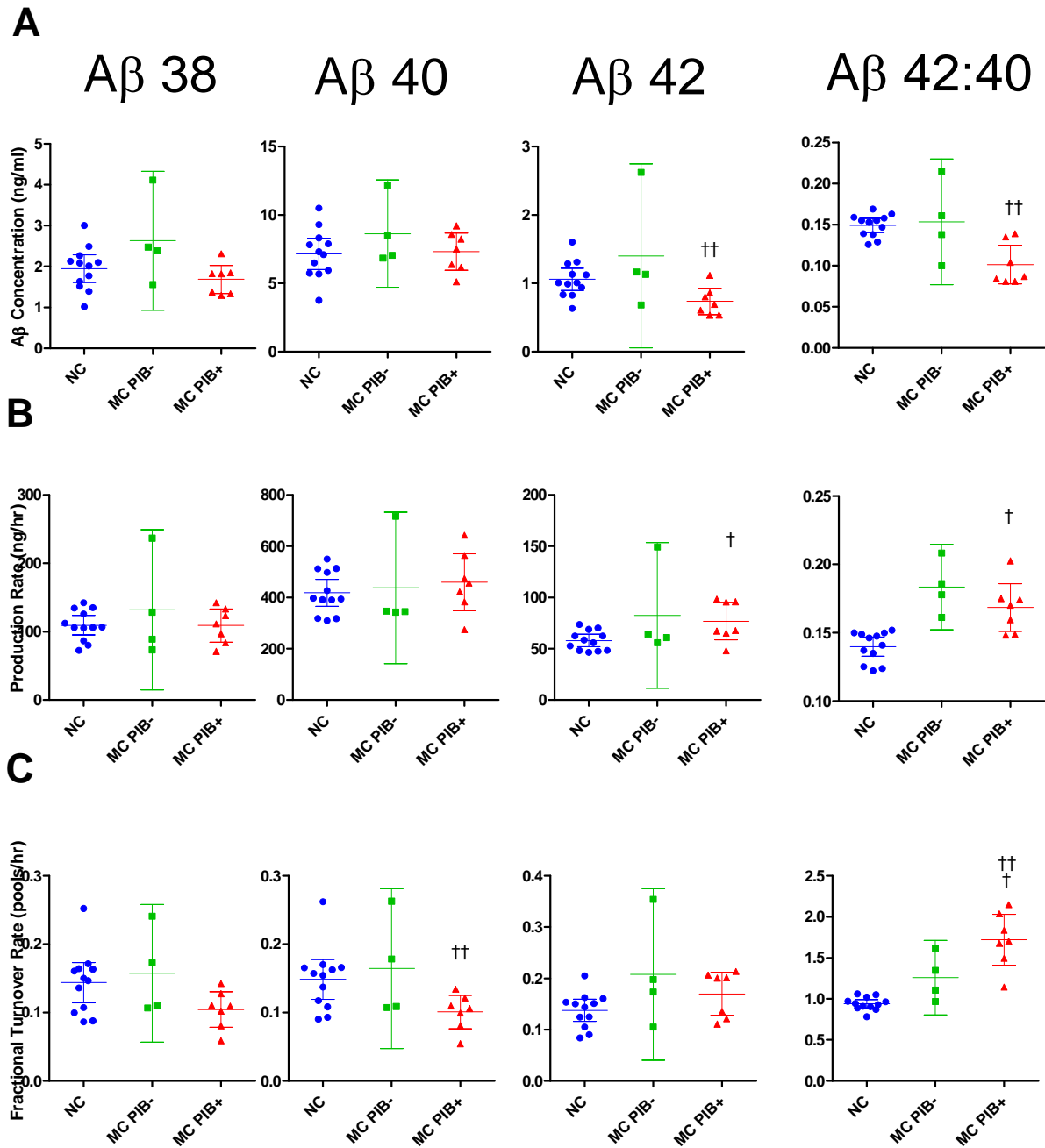
PIB MCBP score = 0.012
A β 42:A β 40 FTR ratio: 1.35
CSF [A β 42]:[A β 40] ratio: 0.138
Exchange of A β 42: Yes



Summary of Mutation carrier PIB- group

PIB MCBP score: -0.001 ± 0.044
A β 42:A β 40 FTR ratio: 1.26 ± 0.29
CSF [A β 42]:[A β 40] ratio: 0.153 ± 0.048
Exchange of A β 42: 3/4

Fig. S7. Scatterplot of concentrations and selected kinetic parameters



Parameters for baseline CSF A β concentrations (A), production rate (B), and fractional turnover rate (FTR) (C) are shown for each individual non-mutation carrier (NC), and for mutation carriers (MC) without (PIB-) or with (PIB+) evidence of amyloid deposition. Each parameter was measured for A β 38 (1st column), A β 40 (2nd column), A β 42 (3rd column) and the A β 42:40 ratio (4th column), and compared by mutation status and amyloid deposition. Error bars indicate 95% CI. Statistical significance based on mutation status (†) and PIB MCBP score (††) are indicated.

Video file: A β 42 and A β 40 Stable Isotope Labeling Kinetic model in the CNS of PS1 and PS2 mutation carriers.

The model compartments for soluble, exchange, and irreversible loss of A β are displayed on a template MRI image with a hypothesized soluble compartment throughout the CNS, and exchange and irreversible loss around fibrillar plaques (in purple). Location of fibrillar plaques was determined using the average PiB image for PiB+ mutation carriers. Note: labeled A β pools have exaggerated spatial scale for visual comparison.



FACS Video 1.mpg