Supporting Information

Benzinger et al. 10.1073/pnas.1317918110

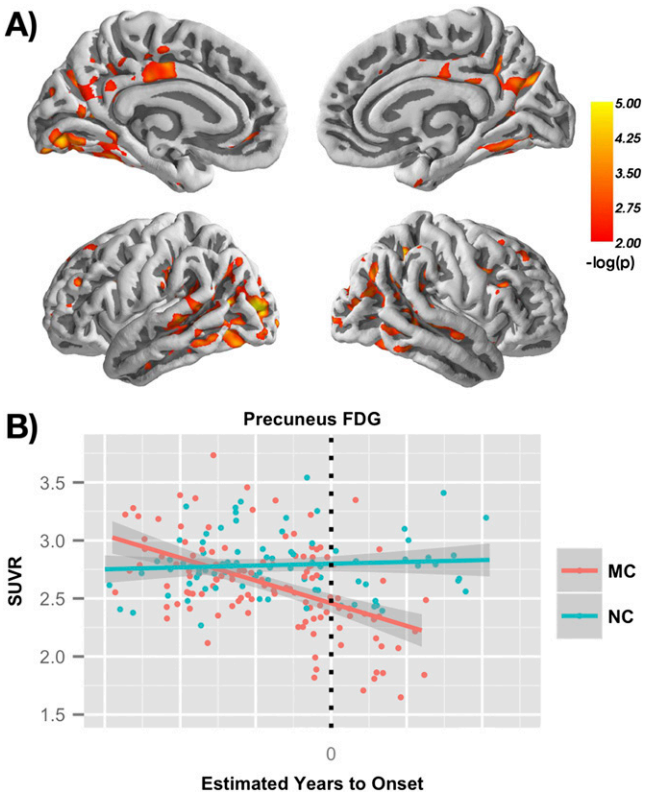


Fig. S1. (*A*) Surface projections of glucose metabolism imaged by fluro-deoxyglucose (FDG) PET 25 y before estimated onset of symptoms. Note the significant regional hypermetabolism in multiple cortical regions in red/yellow. Regions with elevated FDG uptake include the precuneus/posterior cingulate, prefrontal cortex, and the lateral temporal and parietal lobes. (*B*) Scatter plot of regional FDG in the precuneus. Precuneus FDG in carriers decreased to normal levels around estimated years from symptom onset (EYO) = −20 before becoming hypometabolic around EYO = −10. Overlaid on each group's scatter plot are linear regression fits with 95% confidence intervals of the mean in gray. To protect participant mutation status, the *x* axis is unlabeled and uniform noise (minimum = −1, maximum = 1) was added to each EYO value.

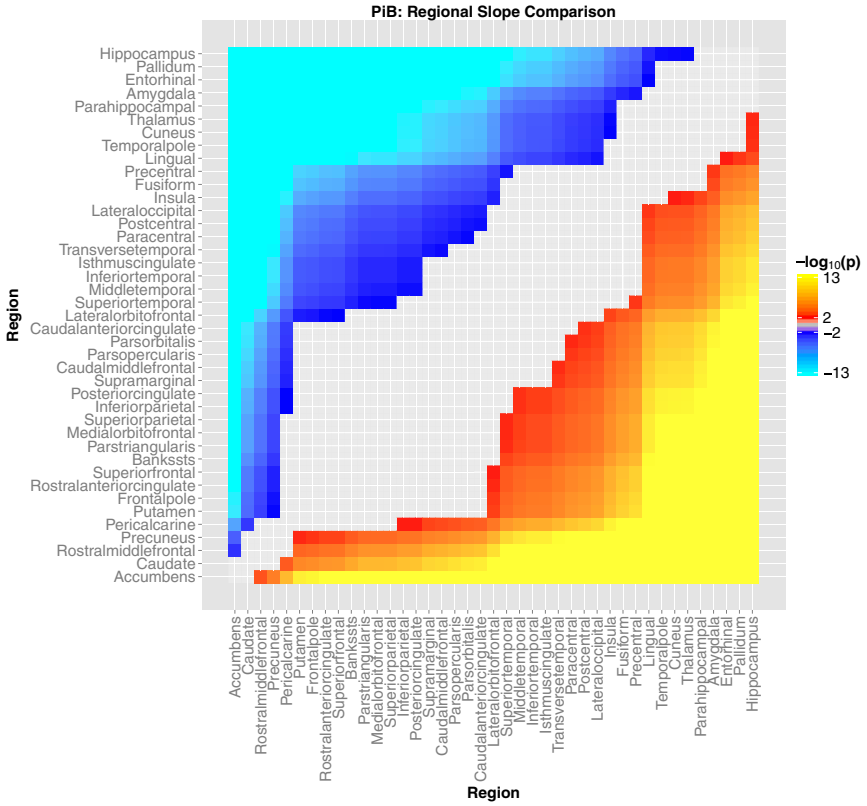


Fig. S2. Comparison of the cross-sectional slopes for regional PiB uptake in mutation carriers. Red/yellow colors indicate cells where the slope of the region on the *y* axis is significantly greater than the region on the *x* axis. Slopes that are significantly less than the *x*-axis region are in blue. Regions are ordered from greatest to smallest slope. All *P* values are corrected for multiple comparisons using false discovery rate (q = 0.05). The greatest rates of amyloid accumulation in the mutation positive group were observed in nucleus accumbens, caudate, rostral middle frontal gyrus, and precuneus. Conversely, the hippocampus and entorhinal cortex showed the lowest rates of amyloid accumulation.

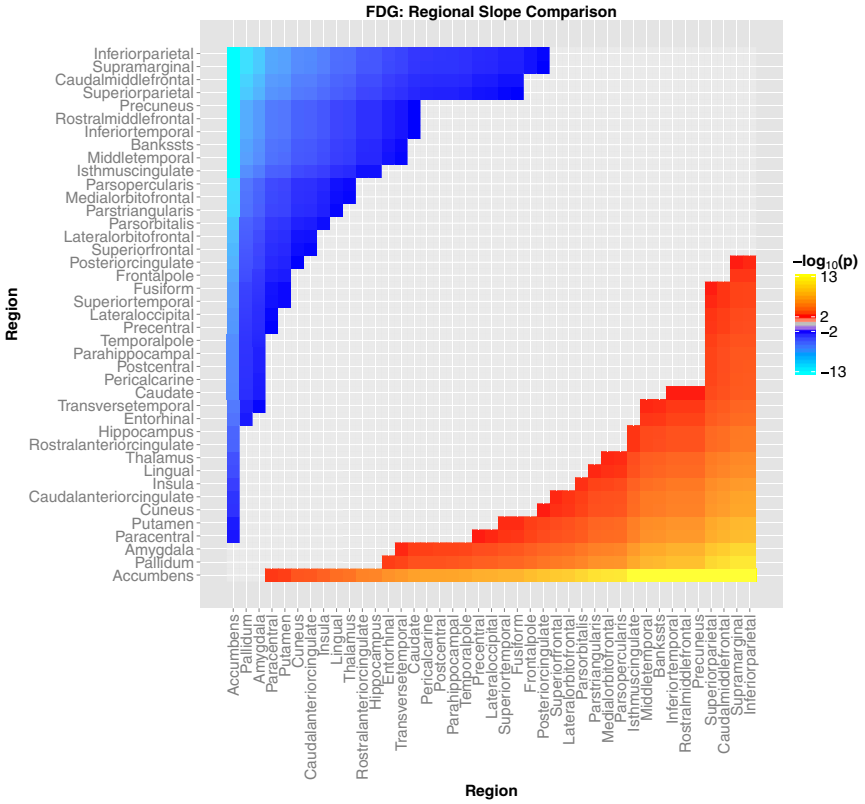


Fig. S3. Comparison of the cross-sectional slopes for each FDG region in mutation carriers. Conventions as in Fig. S1.

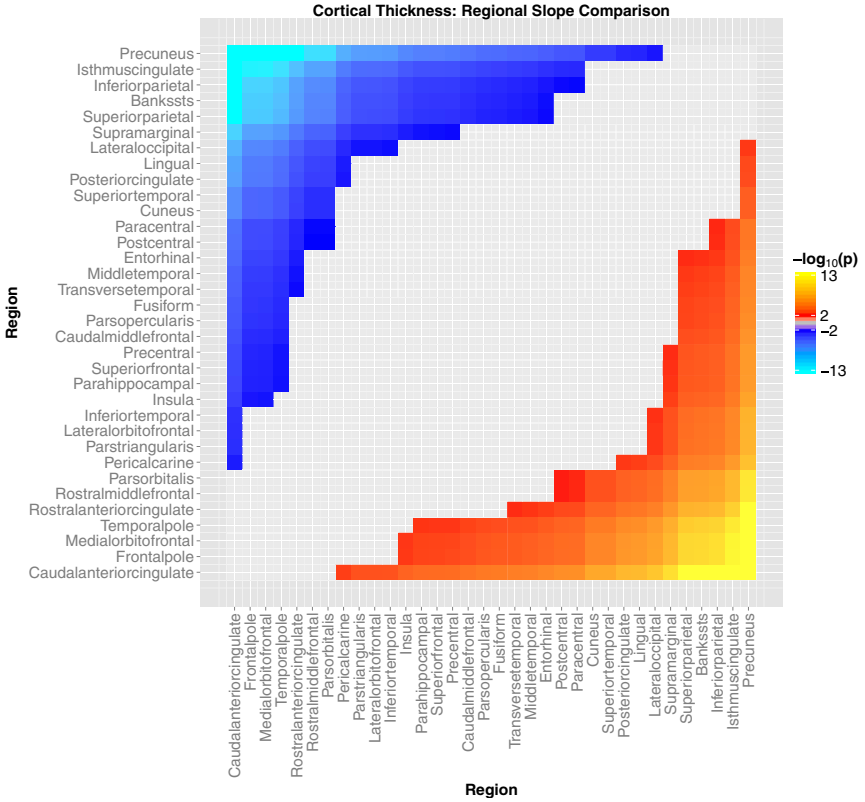


Fig. S4. Comparison of cross-sectional slopes of cortical thickness in autosomal dominant Alzheimer's disease (ADAD)-positive mutation carriers. All conventions as in Fig. S1.

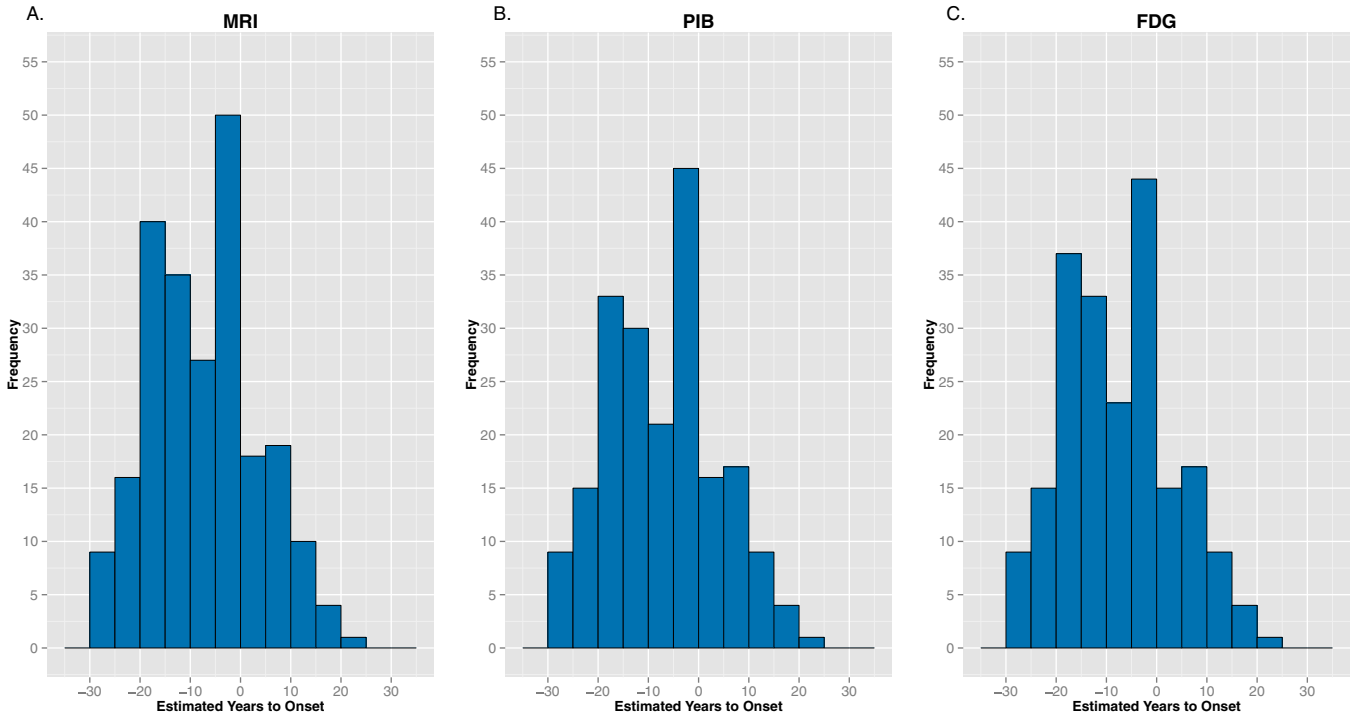


Fig. S5. Number of participants with MRI (*A*), PiB (*B*), and FDG (*C*) scans within 5-y EYO intervals from −30 to 30. Mutation status is not indicated to reduce the likelihood of participants' guessing their genetic status.

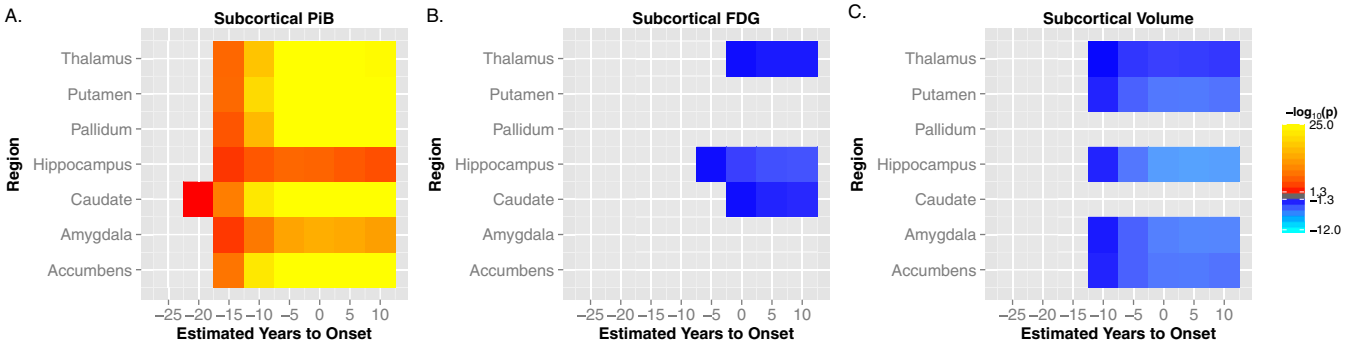


Fig. S6. Comparison of PiB (*A*), FDG (*B*), and volume (*C*) between carriers and noncarriers in subcortical gray matter uncorrected for partial volume effects. Analysis strategy as in Fig. 2.

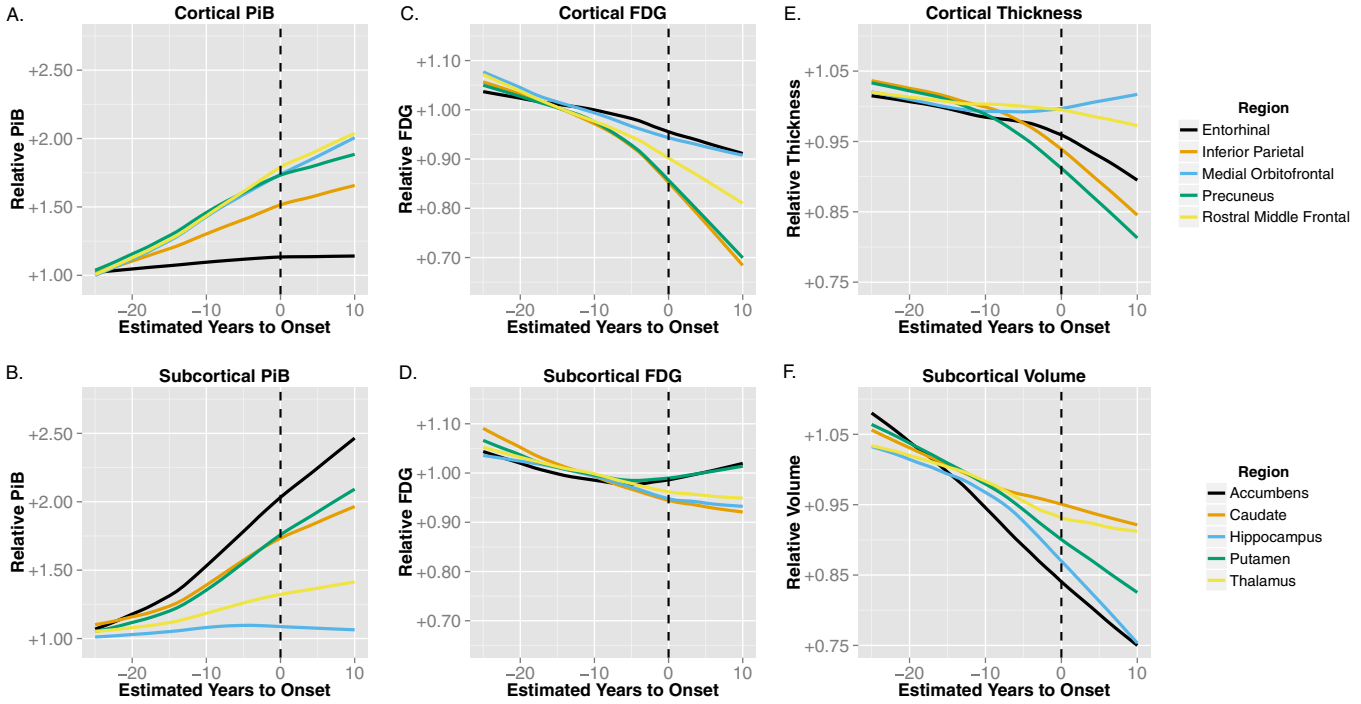


Fig. S7. Biomarker trajectories without partial volume correction for PiB (*A* and *B*), FDG (*C* and *D*), cortical thickness (*E*), and subcortical volume (*F*). All conventions are the same as in Fig. 3.

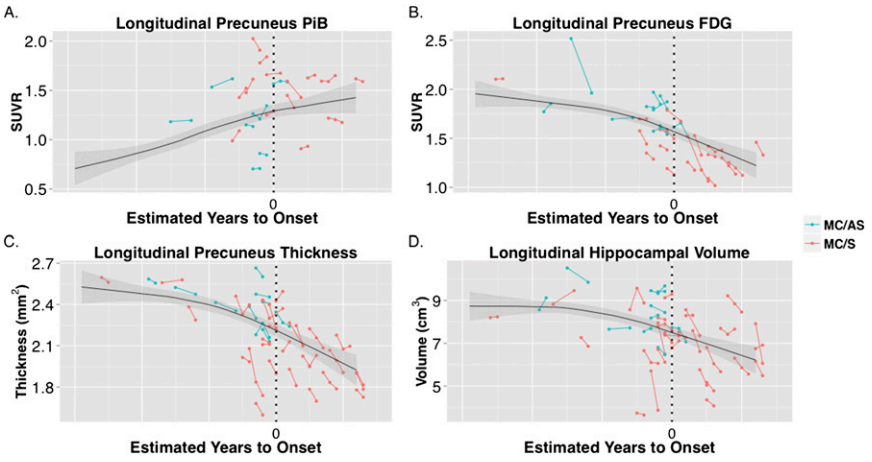


Fig. S8. Longitudinal data for PiB (*A*), FDG (*B*), cortical thickness (*C*), and hippocampal volume (*D*). PET data have not been corrected for partial voluming. Analysis strategy as in Fig. 4.

Table S1. Demographics for participants with longitudinal imaging, separated by mutation and cognitive status

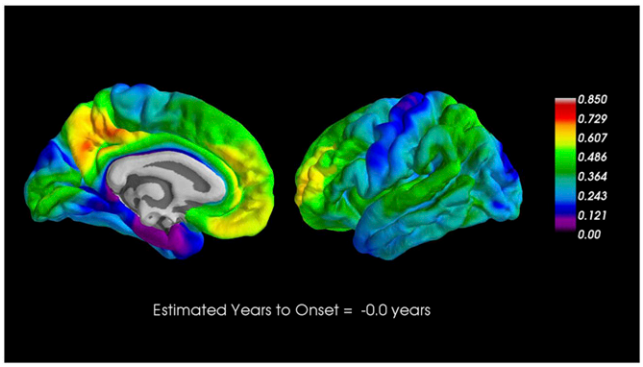
Demographic	Imaging modality											
	MRI				PiB				FDG			
	NC	MC/AS	MC/S	*P* value	NC	MC/AS	MC/S	*P* value	NC	MC/AS	MC/S	*P* value
n	14	10	29	—	10	7	14	—	11	10	19	—
Baseline age (SD), y	39.2 (7.07)	36.8 (9.03)	43.3 (10.4)	0.129	40.9 (6.3)	37.6 (7.72)	43.4 (8.08)	0.251	40.2 (6.43)	36.8 (9.03)	43 (9.97)	0.214
Baseline EYO (SD), y	−4.43 (8.08)	−6 (6.31)	0.069 (8.4)	0.0671	−3.8 (8.42)	−5.14 (5.15)	1.29 (5.37)	0.0657	−3.55 (8.03)	−6 (6.31)	0.316 (7.87)	0.0976
Follow-up time (SD), y	1.86 (0.949)	1.42 (0.793)	1.11 (0.398)	0.16	2.1 (0.994)	1.44 (0.882)	1.12 (0.342)	0.0781	2 (1)	1.42 (0.793)	1.09 (0.294)	0.00399
Education (SD), y	13.7 (1.9)	15 (2.26)	12.8 (2)	1.71E-02	14.4 (1.78)	16.1 (1.57)	12.6 (1.83)	0.00051	14.3 (1.74)	15 (2.26)	12.7 (1.82)	0.0103
Male (%)	7 (50)	5 (50)	15 (51.7)	0.993	3 (30)	3 (42.9)	8 (57.1)	0.442	4 (36.4)	5 (50)	9 (47.4)	0.802
APOE4+	2 (14.3)	6 (60)	8 (27.6)	0.0499	2 (20)	4 (57.1)	5 (35.7)	0.311	2 (18.2)	6 (60)	6 (31.6)	0.128

NC and MC indicate the absence or presence of an ADAD mutation. Mutation-positive individuals whose baseline clinical dementia rating score was greater than zero were classified as symptomatic (MC/S). The remaining mutation carriers were classified as asymptomatic (MC/AS). APOE4+ indicates the presence of the apolipoprotein E4 allele.

Table S2. Estimated longitudinal slopes for precuneus PiB, precuneus FDG, precuneus thickness, and hippocampal volume

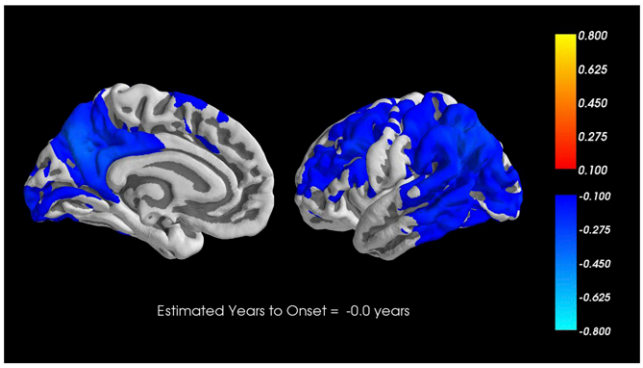
Group	Precuneus PiB, SUVR/y	Precuneus FDG, SUVR/y	Precuneus thickness, mm^2/y	Hippocampal volume, mm^3/y
NC	−0.005 ± (0.042)	−0.053 ± (0.041)	−0.006 ± (0.017)	−25.272 ± (100.868)
M+ asymptomatic	0.040 ± (0.056)	−0.062 ± (0.080)	−0.027 ± (0.032)	−42.572 ± (268.348)
M+ symptomatic	0.049 ± (0.065)	−0.128* ± (0.065)	−0.059*,† ± (0.021)	−352.890*,† ± (164.990)

Data are mean and 95% confidence intervals. SUVR, standardized uptake value ratio.
*Significant ($P < 0.05$, uncorrected) differences from the M− group.
†Trend-level ($P < 0.10$ uncorrected) differences from the M+ asymptomatic group.



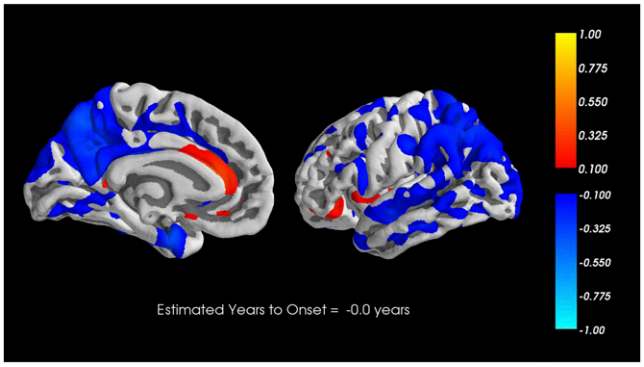
Movie S1. Differences in amyloid accumulation (SUVR) between mutation carriers and noncarriers as measured by PiB PET. Differences were estimated by taking the difference between first-degree locally weighted regression method curves fit to each group's data.

Movie S1



Movie S2. Differences in glucose metabolism (SUVR) between mutation carriers and noncarriers as measured by FDG PET. Analysis strategy as in Movie S1.

Movie S2



Movie S3. Differences in cortical thickness (square millimeters) between mutation carriers and noncarriers. Analysis strategy as in Movie S1.

Movie S3