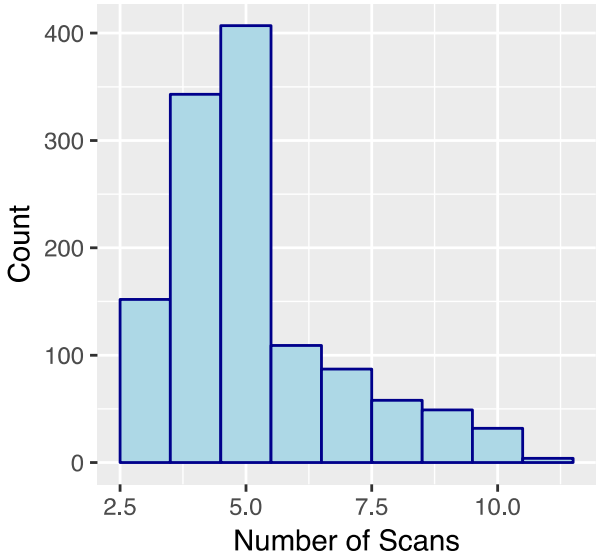
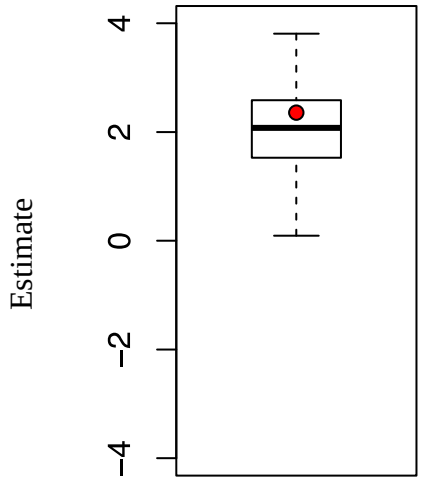
A Longitudinal Imaging Genetics Study of Neuroanatomical Asymmetry in Alzheimer's Disease

Supplemental Information

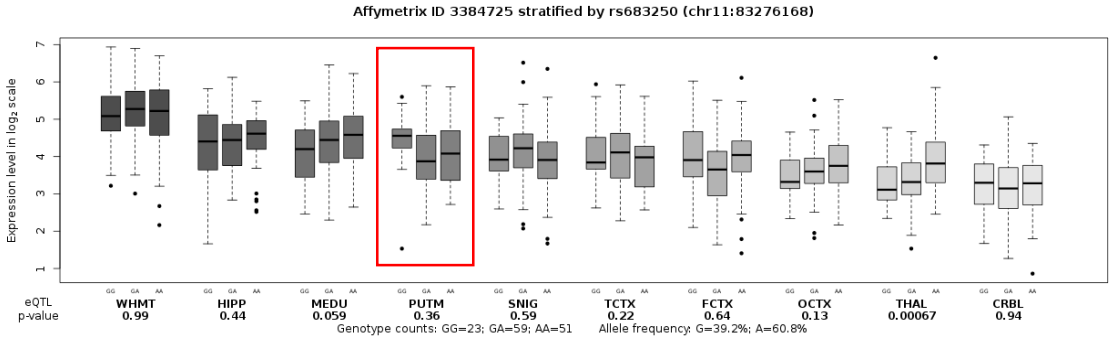


Supplementary Figure S1: Histogram of the number of scans per subject. Most subjects have between four and five scans.

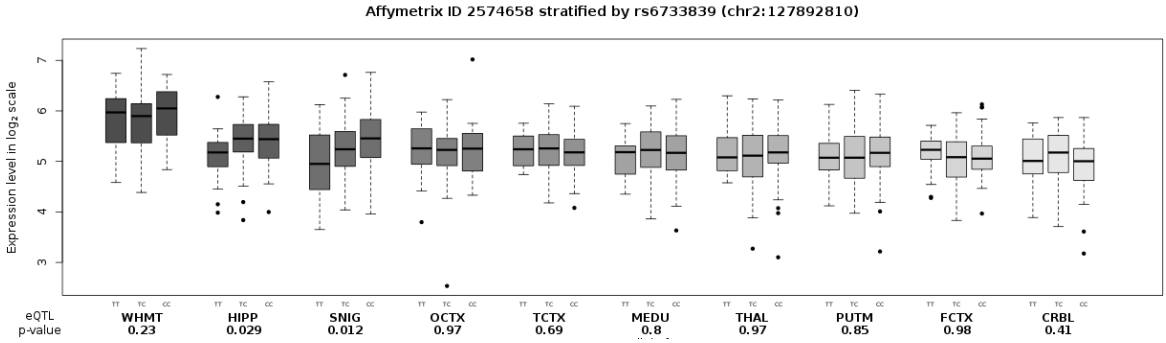


Supplementary Figure S2: Boxplot of estimates for the interaction SNP x diagnosis for SNP rs117253277 and amygdala asymmetry with categorical coding. Matched samples for genotypes CC and CA were created to have a similar number of images per diagnostic group. We used random sampling to generate the matched samples and repeated this procedure 50 times. The estimate of the original model based on unequal sample size is shown as red dot. The median 2.08 and the mean 2.01 are close to the estimate of the original model (2.36).

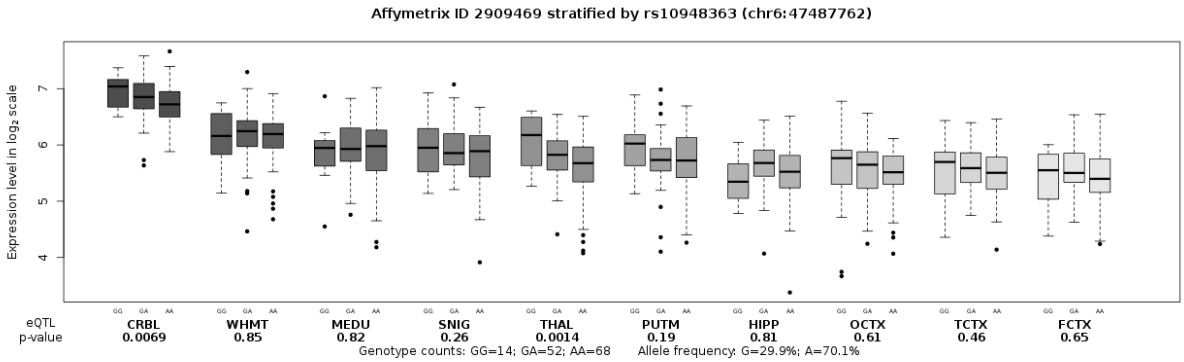
(a) rs683250 and DLG2



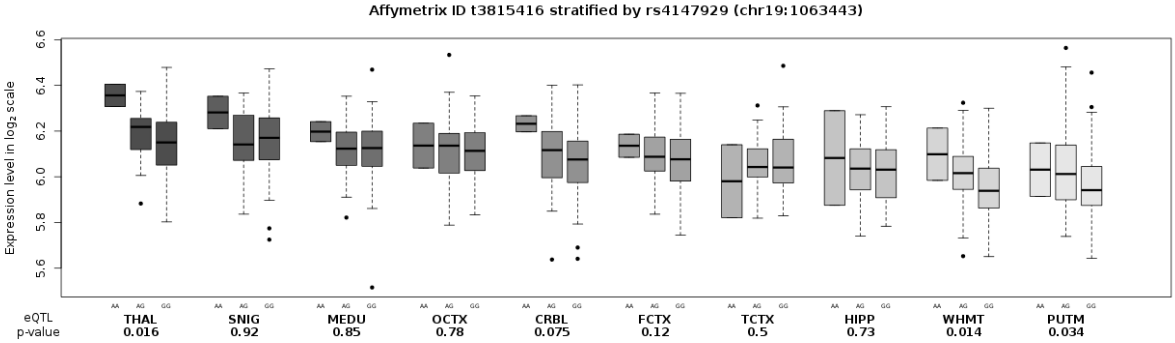
(b) rs6733839 and BIN1



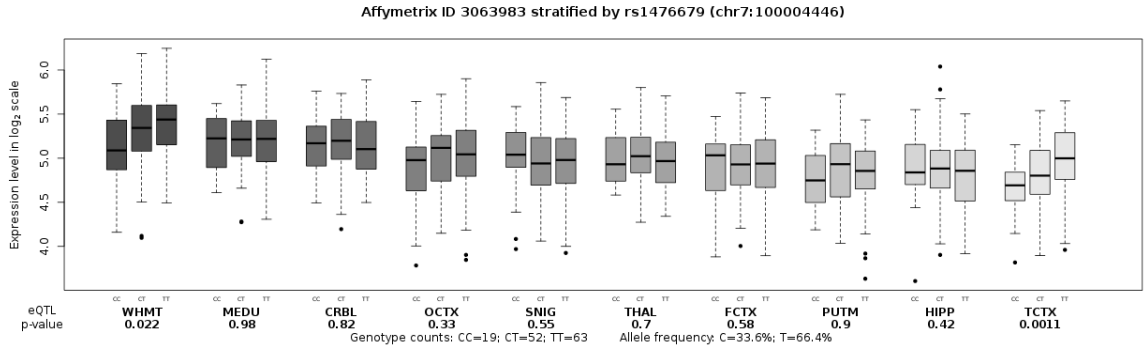
(c) rs10948363 and CD2AP



(d) rs41477929 and ABCA7



(e) rs1476679 and ZCWPW1



Supplementary Figure S3: We studied gene expression quantitative trait loci (eQTL) of significant SNPs using gene expression data from postmortem healthy human brains from the UK Brain Expression Consortium (http://www.braineac.org/). The project analyzed up to 10 brain regions for 134 individuals: cerebellar cortex (CRBL), frontal cortex (FCTX), hippocampus (HIPP), medulla (specifically inferior olivary nucleus, MEDU), occipital cortex (specifically primary visual cortex, OCTX), putamen (PUTM), substantia nigra (SNIG), thalamus (THAL), temporal cortex (TCTX) and intralobular white matter (WHMT).

The plots show the gene expression levels stratified by genotypes of the corresponding SNP. Most of our findings were for SNP x diagnosis interactions; only rs10948363 and rs683250 showed a significant main effect SNP. Since expression data was collected on healthy subjects, we only expect differences for SNPs with significant main effect. rs10948363 was associated to amygdala asymmetry, but amygdala was not included in the eQTL mapping analysis. This only leaves SNP rs683250, which was associated to putamen asymmetry. In plot (a), we observe higher expression levels of DLG2 for GG than for GA or AA in putamen (red box). For completeness, we also include results for *cis*-eQTL mapping analysis for the other SNPs (b) – (e), except for rs117253277, which was not part of the Braineac database.

Supplementary Table S1: Diagnostic and demographic information of the ADNI sample used for the experiments.

Diagnosis	
Total	*1,241*
Controls	434
MCI-stable	367
MCI-progressor	269
AD	171

Age	
Mean	75.9
SD	6.9
Minimum	59.6
Maximum	95.0

Sex	
Female	504
Male	737

Years of education	
Mean	16.4
SD	2.5

Supplementary Table S2: Standardized regression coefficients and *p*-values for the analysis of lateral asymmetry with genetic loci for the linear mixed effects model without interactions. Adjusted p-values for the main effect SNP are presented, where we only show significant associations after FDR correction. *p*-values are rounded to five decimal places. The diagnosis is modeled as categorical variable, where we only report difference between CN and AD. The other factors were not significant.

		β_3 (SNP)			β_4 (Diagnosis) CN->AD	
SNP	GWAS	Beta	P-value	Adj. P-value	Beta	P-value
Amygdala asymmetry						
rs10948363	AD	-0.114	0.00027	*0.00824*	0.335	0.00000
Putamen asymmetry						
rs683250	Putamen	0.110	0.00058	*0.01786*	0.107	0.00000

SNP List

List of 31 SNPs used in this study. 21 candidate AD SNPs (1):

rs6656401, rs6733839, rs10948363, rs11771145, rs9331896, rs983392, rs10792832, rs4147929, rs9271192, rs28834970, rs11218343, rs10498633, rs8093731, rs35349669, rs190982, rs2718058, rs1476679, rs10838725, rs17125944, rs7274581, rs3865444

10 SNPs with association to subcortical brain structures taken from (2) based on a cut-off of p<1 x 10-7:

rs1318862, rs77956314, rs61921502, rs945270, rs62097986, rs6087771, rs683250, rs17689882, rs117253277, rs16944686

Implementation details of the linear mixed effects model

We use the lme4 package (3) in R for implementing the mixed effects model and compute *p*-values with the lmerTest package (4). The model is fitted with restricted maximum likelihood. The Satterthwaite approximation is used for the computation of the *p*-values, which offers advantages over the likelihood ratio test and applying the z distribution to the Wald t values from the model output (5). It was further observed in simulation studies that the Kenward-Roger and Satterthwaite approximations produced the most consistent Type 1 error rates (5). To confirm the computed *p*-values, we also used the more computationally intense Kenward-Roger approximation, but the results were very similar (identical up to the fifth decimal place). In addition, we performed permutation tests that confirmed the robustness of the significance estimates. We used the R package predictmeans, which implements permutation tests for linear mixed effects models (lme4), with 50,000 repetitions.

Supplemental References

1. Lambert J-C, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013;45(12):1452–8.

2. Hibar DP, Stein JL, Renteria ME, Arias-Vasquez A, Desrivières S, Jahanshad N, et al. Common genetic variants influence human subcortical brain structures. Nature. 2015;520(7546):224–9.

3. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. ArXiv Prepr ArXiv14065823. 2014;

4. Kuznetsova A, Brockhoff PB, Christensen RH. lmerTest package: Tests in linear mixed effects models. J Stat Softw. 2017;82(13):1–26.

5. Luke SG. Evaluating significance in linear mixed-effects models in R. Behav Res Methods. 2017;49(4):1494–502.