Longitudinal Study of Genetic Influence of APOE e4 on Hippocampal Atrophy with Conformal Geometry

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Introduction

The apolipoprotein E (APOE) e4 genotype is the most prevalent known genetic risk factor for Alzheimer's disease (AD), so APOE genotyping is considered critical in clinical trials of AD. Here we examined the longitudinal effect of APOE e4 on hippocampal morphometry.

Methods

1. All T1-weighted images were segmented with FSL/FIRST.
2. Hippocampal surfaces were reconstructed from the segmentations.
3. Conformal parameterizations of hippocampal surfaces were computed with holomorphic 1-form.
4. Point-to-point correspondences between hippocampal surfaces were computed by the inverse consistent fluid registration method, which was extended to work with general surfaces [1].
5. Surface deformations were measured by new multivariate statistics [2] consisting of radial distance and multivariate tensor-based morphometry (mTBM).
6. Permutation tests were used to perform group comparisons.

Experiments

The 6 month consisted of adults, ages 55 to 90, including 214 elderly healthy controls (CTL), 359 subjects with mild cognitive impairment (MCI) and 165 AD patients. The 12 month dataset consisted of 203 CTL, 338 MCI and 144 AD. The 24 month dataset consisted of 178 CTL, 254 MCI and 111 AD. Subjects carrying no ApoE e4 allele (e3/e3) are called ApoE e4 noncarriers. Subjects carrying 1 ApoE e4 allele (e3/e4) are called heterozygous ApoE e4 carriers and subjects carrying 2 ApoE e4 alleles (e4/e4) are called homozygous carriers.

1. ApoE e4 carriers (e3/e4 and e4/e4) versus noncarriers (e3/e3) in the full ADNI cohort, as shown in Fig.1, (a) $p<0.0001$, (b) $p < 0.0001$, (c) $p < 0.0005$.

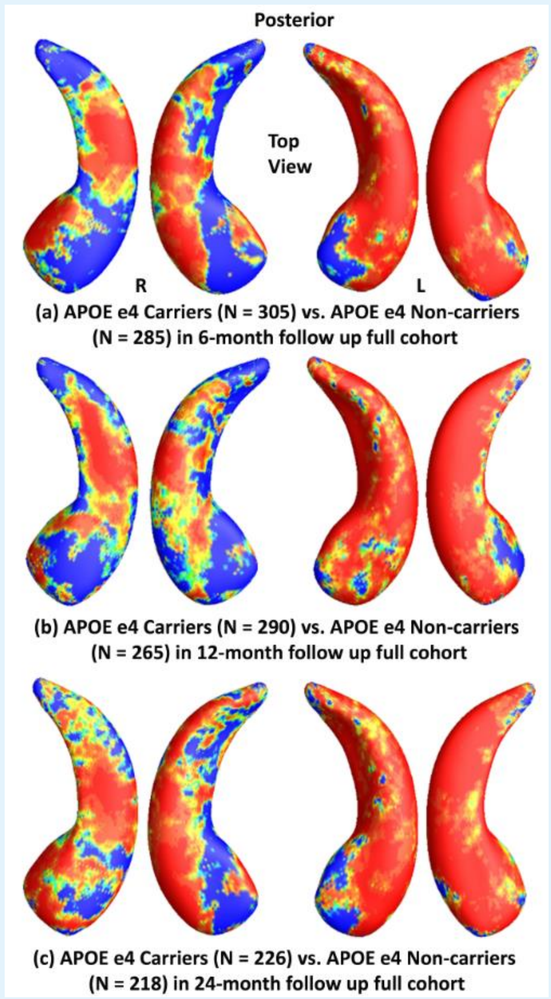


Figure 1. Illustration of local shape differences (p-values) between the ApoE e4 carriers (e3/e4 and e4/e4) and noncarriers (e3/e3) in the full ADNI cohort.

2. ApoE e4 heterozygous carriers (e3/e4) versus noncarriers (e3/e3) in the full ADNI cohort, as shown in Fig.2, (a) $p<0.0116$, (b) $p < 0.0039$, (c) $p < 0.0003$.
3. ApoE e4 homozygous carriers (e4/e4) versus noncarriers (e3/e3) in the full ADNI cohort, as shown in Fig.3, (a) $p<0.0001$, (b) $p < 0.0001$, (c) $p < 0.0001$.

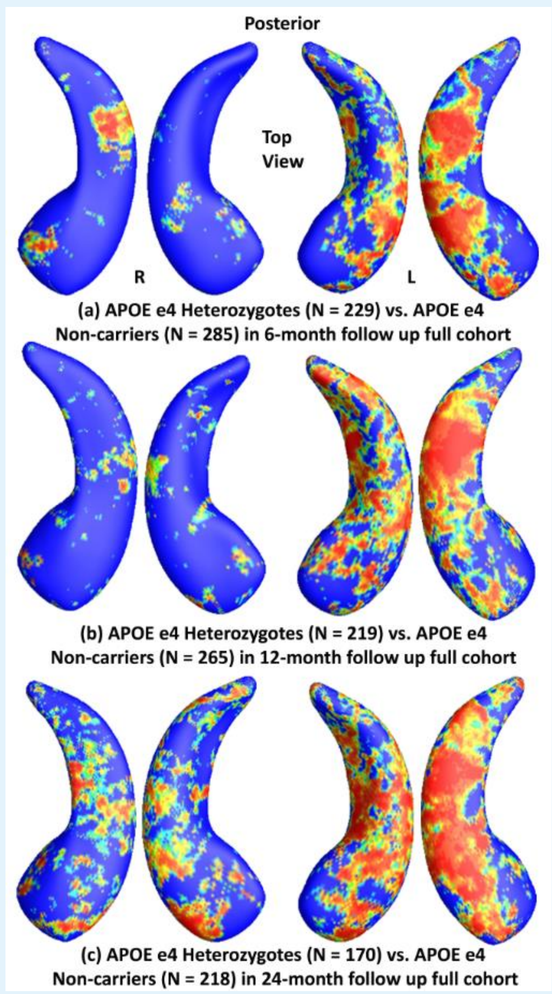
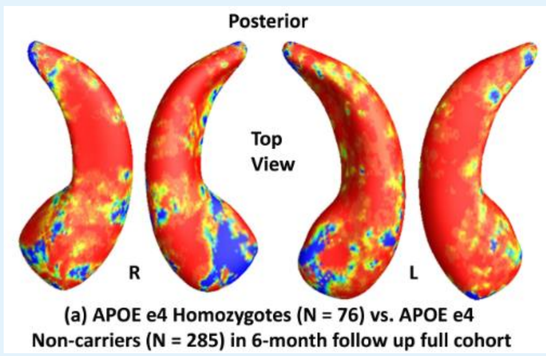


Figure 2. Illustration of local shape differences (p-values) between the ApoE e4 heterozygous carriers (e3/e4) and noncarriers (e3/e3) in the full ADNI cohort.



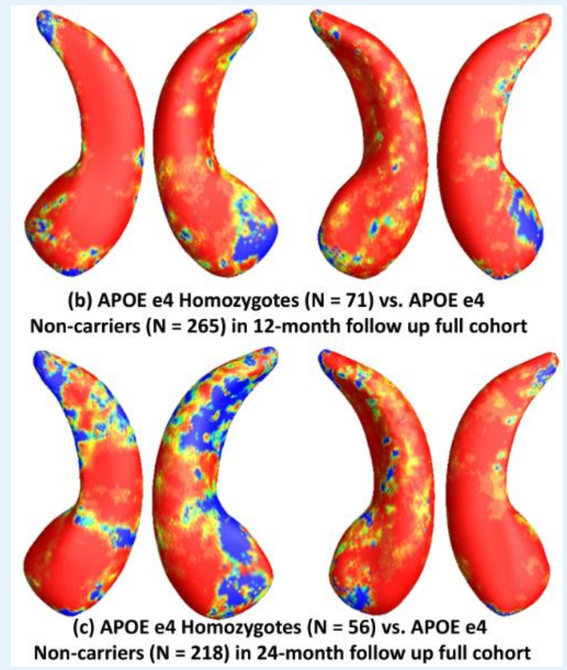


Figure 3. Illustration of local shape differences (p-values) between the ApoE e4 homozygous carriers (e4/e4) and noncarriers (e3/e3) in the full ADNI cohort.

Conclusion

Our analyses revealed significant differences between APOE e4 carriers and noncarriers in all three follow up cohorts, between e4 homozygous and heterozygous in the 6- and 12-month follow up cohorts, between e4 homozygous and non-carriers in all three follow up cohorts, and between e4 heterozygotes and non-carriers in all three follow up cohorts. We found carrying more APOE e4 copies was associated with greater longitudinal hippocampal atrophy.

References

1. Shi, J. et al, 2013. Surface Fluid Registration of Conformal Representation: Application to Detect Disease Burden and Genetic Influence on Hippocampus. NeuroImage, 78:111-134.
2. Wang, Y. et al, 2011. Surface-based TBM Boosts Power to Detect Disease Effects on the Brain: An N=804 ADNI Study. NeuroImage, 56(4):1993-2010.