Voxel-based morphometery to detect the effect of APOE on brain grey matter changes in Parkinson's Disease

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Target audience Neurologists and neuroradiologists interested in the putative role of ApoE in the pathophysiology of Parkinson's disease (PD).

Purpose To determine whether the presence of the APOE ε4 allele modulates grey matter degenerative changes in patients with PD, with or without dementia.

Methods ***Subjects.*** Twenty-five DP patients with the APOE ε4 allele were selected (mean age 63.4 ± SD 7.4; 14 female), of whom 13 had dementia (defined by an adjusted Mini Mental State Examination (MMSE) score < 22), and 24 patients without the ε4 allele (66.1. ± 8.1; 14 female), of whom 12 had dementia. Twenty-six healthy controls (63.5 ± 7.4; 15 female) were also included in the study.

Acquisition protocol. Each subject underwent an MRI brain examination in a 1.5 T GE Signa Horizon NV/i system equipped with a birdcage head RF coil for signal reception, and gradient system providing a maximum gradient strength of 50 mT m^{-1} and maximum slew rate of 150 mT m^{-1} ms^{-1}. A T_1-weighted sagittal volumetric image was acquired using the FSPGR sequence (TI=600 ms; TR/TE=6.7/15.2 ms, FOV 24 cm2, 1.2 mm slice thickness, in-plane resolution 256 x 256).

Analysis protocol. Structural data were analyzed using SPM8 software. Volumes were first segmented pixelwise into gray and white matter, and CSF components. Grey and white concentration maps were jointly aligned and registered by non-linear deformation using the SPM DARTEL tool, to a study specific template created jointly from all subject data. After Gaussian smoothing and affine registration to the MNI-152 template, volumes were intensity normalized by the local jacobian of the deformation map, yielding a tissue 'concentration' value. Whole brain grey and white matter and CSF concentrations were calculated, and total intracranial volume (TIV) defined as the sum of these components.

Testing was performed on gray matter (GM) concentrations, considering as significant $P < 0.05$ corrected for multiple comparisons using the family-wise error rate (FWE). Group comparison of patients and controls was performed voxel-wise based on an ANCOVA model, introducing age, and TIV as covariates.

For patients, we performed an ANCOVA to discern differences between subjects with and without the APO ε 4 allele, with the adjusted MMSE score and TIV as covariates.

For each whole brain tissue volume, patients with and without dementia, and healthy controls were compared using ANOVA, with total intracranial volume and age as covariates. For patients only, subjects with and without APOE ε4 were compared using adjusted MMSE, TIV, and age as covariates.

Results ANOVA revealed that whole brain CSF volume differed between subject groups. In particular PD patients with dementia had a significantly larger tissue volume occupied by CSF compared to controls (estimated mean difference +14.80 mL; p(t)=0.0002), and a smaller grey matter volume (estimated mean difference -9.99 mL; p(t)=0.007). The three subject groups showed no difference in whole brain white matter. Considering only the PD group (Figure 1), subjects with and without the APO ε 4 allele differed, with the former having a greater CSF volume (estimated mean difference -6.97 mL; p(t)=0.031). CSF volume was also increased in subjects with reduced adjusted MMSE (mean estimated change -1.49 mL per scale point; p(t)=0.0014). Whole brain grey and white matter volumes showed no dependence on the APOE allele.

We found no significant differences between patients and controls, or between patients with or without the APOE ε4 allele, with regard to the VBM analysis. In addition there was no correlation with the MMSE score.

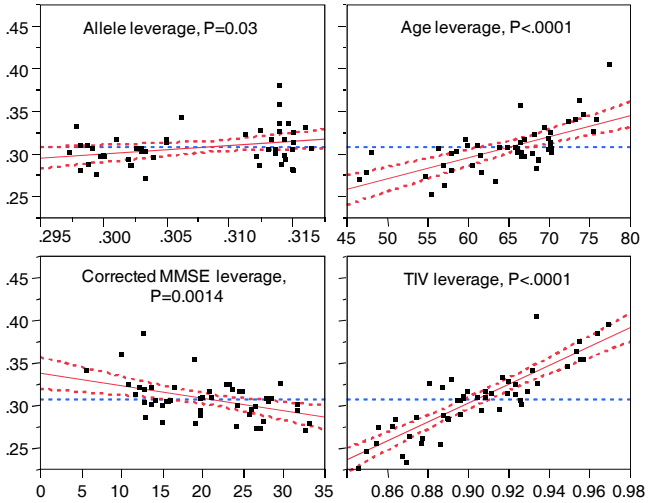

Fig. 1: Leverage plots of whole brain CSF volume (L; ordinate) for PD patients, against potential explanatory variables (abscissa). Red line: imputed regression with 95% confidence intervals.

Discussion Although research on the putative role of ApoE in Parkinson disease (PD) is contradictory and variations in epsilon alleles do not appear to be a direct risk factor for the disease,[1,2] studies do suggest that APOE ε4 is associated with more rapid cognitive decline in PD patients,[3] and the presence of dementia,[4] while in patients without dementia that the presence of the APOE ε4 allele is related to worsening executive function, visiospatial function, activation retrieval, and age-adjusted performance on the MMSE exam.[5] If these observed associations hold more generally, then even after controlling for the presence of dementia, localized brain structural changes might be expected.

However, in a group of PD patients, balanced with respect to APOE allele, and the presence of dementia, we found no such localized changes, either compared to healthy controls, or within the PD study population. Given that the presence of the APO E4 allele was associated with increased CSF volume in the patients, the lack of specific areas of difference might indicate either heterogeneity at the individual level, or slight, diffuse reductions in brain tissue.

Conclusions The present study provides no evidence to support the hypothesis that variations in the APOE epsilon allele are associated with grey matter degenerative changes in patients with Parkinson's disease, either with or without dementia.

References

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