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**Altered grey matter networks in young patients with MS at genetic risk for Alzheimer's disease**

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**Background:** The Apolipoprotein E (*APOE)* $\varepsilon_4$ is the major susceptibility factor for cognitive impairment and Alzheimer's disease. Cognitive decline is also a concern in patients with multiple sclerosis (MS). Whether *APOE* $\varepsilon_4$ exerts an effect on brain structure and grey matter (GM) networks in MS patients that could potentiate the long-term cognitive disabilities is unclear. Moreover the description of the exact link between genetic markers and MR driven measures of brain integrity are of essential importance to study cognition in patients with MS and for interventions to prevent longitudinal deterioration.

**Methods:** MS Patients with no immunomodulatory treatment were enrolled in the "Krankheitsbezogene Kompetenznetz Multiple Sclerosis (KKNMS)". From this multicenter dataset 37 heterozygous *APOE* $\varepsilon_4$ carriers (i.e. having the genotype $\varepsilon_3/\varepsilon_4$) and 37 non-carriers ($\varepsilon_3/\varepsilon_3$) were matched for demographics (mean age: 38.4±9.2 yrs, mean EDSS 1.23±0.99) from one site. A replication study was performed in a cohort (n=46) from a second site. Cortical thickness (CT) was derived from 3T MRI using FreeSurfer. GM connectivity networks were reconstructed from the CT correlation between the 68 regions of the Desikan-Killiany atlas. Cortical integrity and network connectivity -derived from graph theoretical approaches- were compared between the groups in both cohorts. Results corrected for multiple comparisons were considered ($p< 0.05$ FDR).

**Results:** No regional or global cortical atrophy differences were attested between the two groups in both cohorts. In the network connectivity analysis a decreased local connectivity pattern (reduced transitivity, t=-3.24 p=0.008) was evident in *APOE* $\varepsilon_4$ carriers. Regions with decreased connectivity were consistently seen in the medial part of the left temporal lobe. *APOE* $\varepsilon_4$ status was further associated with raised whole brain connectivity, reflected by increased global efficiency (t=4.34 p=0.005) and reduced modularity (t=-2.84 p=0.02). This network pattern was shown in the frontal, parietal and lateral temporal associative cortices. The results were entirely replicated in the second cohort.

**Conclusion:** We found that MS patients at genetic risk for cognitive decline have significant abnormalities of local GM networks and possibly compensatory increased long-range connectivity patterns. Chronic or focal neuroinflammation could lead to behaviourally relevant memory impairments in these patients through a specific break-down of the long-range paths.

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