Global connectivity of the left frontal cortex enhances cognitive reserve in prodromal Alzheimer’s disease

N. Franzmeier¹, M. Ewers¹ & the Alzheimer’s Disease Neuroimaging Initiative*

¹Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians-Universität LMU, Feodor-Lynen Straße 17, 81377 Munich, Germany.

* Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf
**Background:** Previous studies suggest that cognitive reserve (CR), as measured by higher education, allows to maintain cognitive performance relatively well in the presence of Alzheimer’s disease (AD) brain pathology. However, the neural underpinnings of CR are poorly understood. Here we assessed the functional brain changes that support CR in subjects with mild cognitive impairment (MCI). We hypothesized that MCI subjects with higher CR can tolerate more severe FDG-PET hypometabolism at a given level of cognitive performance, and that an increased tolerance of FDG-PET hypometabolism due to high CR can be explained by higher global functional connectivity of the left frontal cortex (LFC).

**Methods:** Our sample comprised 44 subjects with MCI and 24 healthy control (HC) subjects, recruited within the Alzheimer’s Disease Neuroimaging Initiative. We conducted seed-based connectivity analysis in each subject, computing Pearson-Moment correlations of the resting-state fMRI signal between an 8mm spherical ROI in the LFC (BA 6) and each voxel in the grey matter. To yield the global LFC connectivity index, all positive correlations were Fisher z-transformed and averaged across voxels. Using voxel-based regression, we tested whether in MCI subjects, higher education was associated with stronger FDG-PET hypometabolism, controlling for memory performance. In clusters in which this regression yielded significant results, we tested whether FDG-PET was reduced compared to HC subjects. In further regression analyses, we tested whether higher global LFC connectivity was associated with higher education and reduced effects of FDG-PET hypometabolism onto episodic memory (interaction FDG-PET metabolism x global LFC connectivity).

**Results:** Higher education was associated with stronger precuneus FDG-PET hypometabolism in MCI, when controlling for composite memory scores. Group comparison revealed that precuneus FDG-PET metabolism was reduced in MCI when compared to HC subjects. This suggests that MCI subjects with higher CR can better cope with pathological FDG-PET hypometabolism. Higher education was associated with higher global LFC connectivity in MCI subjects. The interaction global LFC connectivity x precuneus FDG-PET was significant in MCI (p<0.05), such that at higher levels of LFC global connectivity the association between precuneus FDG-PET hypometabolism and memory impairment was attenuated, suggesting compensatory effects of global LFC connectivity.

**Conclusions:** Higher global LPFC connectivity may contribute to higher CR and compensate FDG-PET hypometabolism in MCI, thus allowing to maintain memory performance relatively well in the face of brain pathology.