Cognitive Reserve in Amyotrophic Lateral Sclerosis: a 2-[^{18}F]FDG-PET study on sex-related differences

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Introduction and aim

Cognitive Reserve (CR) mechanisms have been hypothesised to explain the discrepancy between neuropathological findings and clinical phenotype in patients with dementia. In a previous study we showed the applicability of the concept of CR to cognitive impairment associated with ALS, particularly the role of education as CR proxy. In this study we aimed to evaluate the possible influence of sex on reserve mechanisms.

Methods

We compared brain 2-[^{18}F]FDG-PET metabolism of male (m-ALS, n=95) and female (f-ALS, n=95) patients, matched for age, education, onset, and King's stage, with no significant difference in ECAS scores. In each group, clusters showing a negative/positive correlation with education were used as *seed regions* in an interregional correlation analysis (IRCA) to evaluate brain metabolic connectivity. We identified the *seed regions* including age, onset, King's stage and ECAS as covariates.

Results

In the direct comparison between f-ALS and m-ALS we identified a relative hypometabolism in m-ALS in clusters including extensive bilateral frontotemporal regions, as well as more limited right parieto-occipital regions.

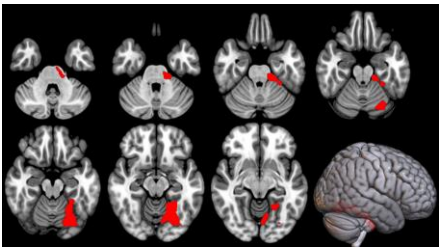

Figure 1. The regions showing a statistically significant positive correlation between brain metabolism and education in f-ALS are marked in red. The clusters are reported on axial sections of a brain Magnetic Resonance Imaging template and on the brain surface of a glass brain rendering (bottom right).

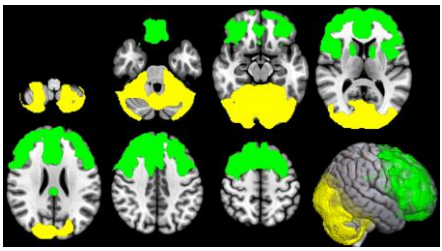

Figure 2. IRCA in f-ALS: clusters showing a statistically significant positive (marked in yellow) and negative (marked in green) correlation with the *seed region* are reported on axial sections of a brain Magnetic Resonance Imaging template and on the brain surface of a glass brain rendering (bottom right).

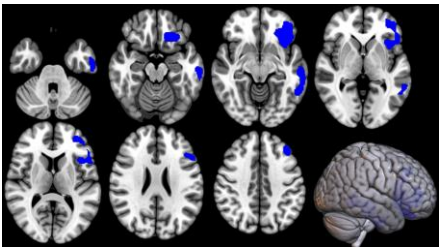

Figure 3. The regions showing a statistically significant negative correlation between brain metabolism and education in m-ALS are marked in blue. The clusters are reported on axial sections of a brain Magnetic Resonance Imaging template and on the brain surface of a glass brain rendering (bottom right).

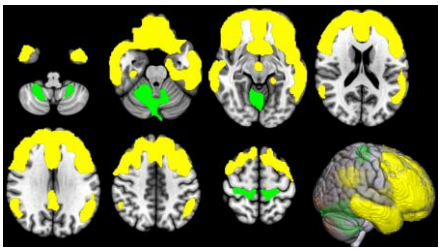

Figure 4. IRCA in m-ALS: clusters showing a statistically significant positive (marked in yellow) and negative (marked in green) correlation with the *seed region* are reported on axial sections of a brain Magnetic Resonance Imaging template and on the brain surface of a glass brain rendering (bottom right).

Discussion

Our study confirms the validity of the CR hypothesis for the cognitive impairment associated with ALS and highlights that sex can contribute to the heterogeneity of reserve mechanisms in this context. We warrant further studies to elucidate the interplay between sex and other demographic, genetic and social factors, including age, presence of genetic mutations, occupation and leisure activities, in determining CR in ALS patients.

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