

Cognitive Reserve modulates the default mode network in patients with MCI and AD

Marco Bozzali¹, Claire Dowling², Laura Serra¹, Barbara Spano¹, Carlo Caltagirone^{3,4}, and Mara Cercignani⁵

¹Neuroimaging Laboratory, IRCCS Santa Lucia, Rome, Italy, ²School of Life Sciences, University of Sussex, Brighton, United Kingdom, ³Dept of Clinical and Behavioural Neurology, IRCCS Santa Lucia, Rome, Italy, ⁴Dept. of NeuroScience, University of Rome "Tor Vergata", Rome, Italy, ⁵CISC, Brighton & Sussex Medical School, Brighton, United Kingdom

Purpose

Despite the neuropathology of Alzheimer's disease (AD) is well characterized (1), the abnormalities typical of AD may also be detected in the brain of normally functioning elderly individuals (2), and their severity does not always fit with measures of cognitive functioning in AD patients. One of the factors believed to impact on the brain resilience to pathological damage is the so-called "cognitive reserve" (CR), which postulates the existence of brain mechanisms able to cope with cerebral damage (3). These mechanisms are believed to rely on pre-existing cognitive processes or to enlist compensatory processes. We postulated that one of these compensatory mechanisms might rely on an increase in the connectivity within specific functional networks of the brain. The default model network (DMN) is of particular interest as it is known to be involved in cognitive tasks, and also to be altered in patients with AD (4). The aim of this study was to assess the impact of some proxies of CR, estimated using individual data on formal education and occupation, on functional connectivity of the DMN in a cohort of patients with AD or amnesic mild cognitive impairment (a-MCI).

Methods

Participants: Twenty-nine patients, 11 with a diagnosis of probable AD (M/F=4/7; mean age=74.6, SD=6.2 years) and 18 with a diagnosis of amnesic mild cognitive impairment (a-MCI, M/F=8/10; mean age=68.9, SD=9.6), were enrolled for this study. Local Ethical Committee approval and written informed consent were obtained before study initiation. All recruited patients underwent an extensive neuropsychological battery (5). **CR assessment:** All participants were administered a questionnaire to assess the activities performed during life which are likely to impact on cognitive reserve. These include: the level of education (measured by the number of years of school and university attendance), the type of school and university degree obtained, and the main occupation (quantifying the number of years they performed the job and the type of job). For education, 2 categories of high school were modelled (technical and academic), and 2 categories were modelled for university degrees (scientific and humanistic). These categories were combined with the years of formal education using multiple correspondence analysis (MCA), a statistical approach to transform nominal categorical data into numerical scores, to obtain an education score. For occupation, the type of job was classified according to 5 categories defined by the National Institute for Statistics. MCA was used to combine these categories with the number of years that job was done, to obtain an occupation score. A linear regression of each score vs. age was performed and the residual was transformed into a Z-score and retained for further analysis. **MRI:** All patients underwent an MRI examination at 3T, including the following acquisitions: 3D Modified-Driven-Equilibrium-Fourier-Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms); and T2* weighted echo planar image (EPI) sensitised to blood oxygenation level dependent imaging (BOLD) contrast (TR: 2080 ms, TE:30 ms, 32 axial slices) for resting state fMRI. BOLD EPIs were collected during rest for a 7 min and 20 s period, resulting in a total of 220 volumes. During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. **Image Analysis:** RS fMRI data were processed using Matlab7 and SPM8 for image preprocessing and statistical comparison, and the Group Independent Component Analysis (ICA) for fMRI Toolbox (GIFT, icatb.sourceforge.net/) for ICA. The preprocessing steps included correction for head motion, compensation for slice-dependent time shifts, normalisation, and filtering by a phase-insensitive band-pass filter (pass band 0.01–0.08 Hz) to reduce the effect of low frequency drift and high frequency physiological noise. Finally, smoothing with a 3D Gaussian Kernel with 8 mm³ FWHM was applied. ICA analysis was employed to identify 20 independent components. Results were converted to Z-scores, and the DMN was identified (Fig 1). The second level analysis was then performed in SPM8 using a factorial analysis, for each score separately. The factor was the group (aMCI and AD), with a covariate of interest (the score). Age, grey matter total volume, and MMSE were entered as covariates of no interest to adjust the analysis for these potential confounds. Results were accepted as significant at $p < 0.05$ FWE corrected at cluster level (cluster formed with $p < 0.001$ at uncorrected level).

Results

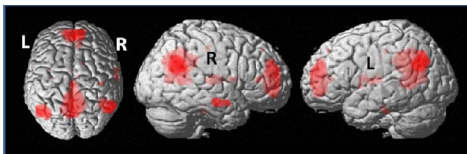


Fig 1. Group-averaged DMN

Neither score (education and occupation) was significantly different between AD and aMCI patients. The Education score was positively correlated with functional connectivity within the DMN ($p=0.003$) across the whole population in the precuneus (Fig 2A). A trend to significance ($p=0.078$) was found for the positive correlation between DMN functional connectivity and the occupation score in the left caudate (Fig 2B).

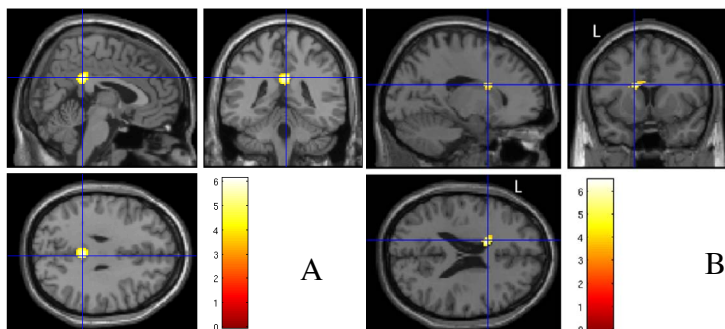


Fig 2. Significant positive association between DMN functional connectivity and "education score" across subjects (A). Positive association between DMN functional connectivity and "occupation score" across subjects (B).

Discussion

Our data confirm that CR has an impact on brain connectivity in mitigating the effects of AD pathology. Modulation of connectivity occurs in one of the most critical nodes of the DMN, i.e. the posterior cingulate, for which disconnection with the medial temporal lobes through the cingulum has been hypothesised to play a critical role in the conversion from MCI to AD (6). In this view, patients with higher education levels and, at a lesser extent, higher occupation scores seem to cope better with AD pathology thanks to phenomena of brain plasticity. Interestingly, the most beneficial effects of CR seem to occur in early phases of life. This is conceivable, as the brain tissue is likely to be more responsive to external stimuli before the occurrence of damage, or up to a stage where its accumulation is minimal. On the other, this would suggest that applying cognitive rehabilitation programs to subjects who are already symptomatic for cognitive decline may bring little advantage. Nevertheless, our results indicate that prevention strategies might have a strong impact in delaying the clinical symptoms of dementia.

References: 1. Braak and Braak, *Neurobiol Aging* 1995;16:271–278. 2. Mortimer, et al., *J Geriatr Psychiatry Neurol* 2005;18:218–223. 3. Stern, J Int Neuropsychol Soc 2002;8:448–460. 4. Greicius, et al. *Proc Natl Acad Sci USA* 2004;101:4637–42. 5. Serra et al. *J Alzheimers Dis* 2010;19:147–59. 6. Gili, et al., *J Neurol Neurosurg Psychiatry*. 2011; 82:58–66.