

# PARIETAL WHITE MATTER LESIONS INCREASE THE RISK OF CONVERSION TO AD IN PATIENTS WITH AMNESTIC MCI AND HIGHER LEVELS COGNITIVE RESERVE.

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**Purpose:** The “cognitive reserve hypothesis” (CR) was proposed to explain the differences among individuals in their ability to cope with physiological or pathological cognitive decline, especially in neurodegenerative condition such as Alzheimer Disease (AD) [1,2]. Aim of the present study was to investigate whether different levels of CR and its interaction with grey matter (GM) atrophy and white (WM) matter abnormalities may contribute in postponing the time-point of inflection toward dementia. **Methods:** forty-two patients with amnesic Mild Cognitive Impairment (a-MCI) [3] were recruited and followed-up for 24 months. At baseline, each patient underwent MRI at 3T collecting the following sequences: 1) Morphological 3D-T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) (TE=2.74 ms, TR=2500ms, Flip angle=8°; matrix=256 x208x176); 2) Fluid attenuated inverse recovery- FLAIR (TR=8170ms, TE=96ms). T1-w scans were assessed to evaluate the severity of GM atrophy, using the Medial Temporal Lobe Atrophy (MTA) scale [4], while FLAIR images were used to assess the severity of WM lesions using the Age Related White Matter Changes (ARWMC) scale [5]. Each patients underwent a questionnaire devoted to assess the level of CR. Quantitative scores, such as the level and type of education, the main occupation, and the principal leisure activities performed in youth and adulthood were derived and used to compute a global enrichment index (G.E.I) as proxy measure of CR. On the basis of their mean G.E.I. value, patients were divided in those with low (LCR) and those with high CR (HCR). Additionally, during follow-up, all patients were neuropsychologically reassessed at six months intervals, and clinically reclassified in MCI converters and non-converters. To investigate the interactions between different levels of CR and the risk for developing AD, we employed the Cox’s regression models and Kaplan-Meier curves. Cognitive performances, MTA and ARWMC scores were entered as regressors in survival analyses. **Results:** After 24 months of follow-up, 18 out of 24 MCI patients converted to AD. No significant difference was observed between MCI converters and non-converters for the following variables: MMSE scores, age, gender distribution, single or multiple domain impairment at baseline. Survival analyses showed the MMSE as the only cognitive score significantly associated to conversion in both, LCR and HCR groups, showing an increased relative risk ratio of AD conversion (RR= 1.84) in patients with LCR as compared to those with HCR (RR= 1.3). When investigating the interaction between CR and brain abnormalities, we found a significant increased risk for developing AD (RR= 34.5) in HCR patients, whose WM lesions were all localized in the left parietal lobe. Additionally, we found an interaction between individual CR and level of cognitive impairment in modulating the mean time of conversion from a-MCI to AD (Figure 2). Specifically, a-MCI patients with higher CR and MMSE scores at baseline, on average, converted to AD one year later than all other recruited patients.

Figure 1

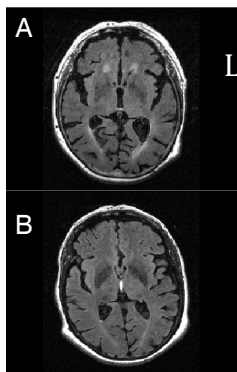


Figure 1. Panel A shows a case of a-MCI patient with HCR and WM lesions localized in the left parietal lobe, compared (Panel B) to a-MCI patient with HCR without WM lesions in the same brain area.

Figure 2

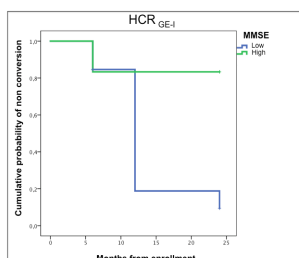


Figure 2. A-MCI patients with high CR and high baseline MMSE, converted to AD significantly later (mean months: 21.0) than those with high CR but lower baseline MMSE score (mean months: 13.3).

**Discussion:** The present study confirms an effect of CR in modulating the risk of conversion from MCI to AD. Moreover, this study clarifies, in patients with a-MCI, the relationship between CR, GM and WM involvement, and quantifies the temporal delay for the conversion to dementia. This strongly suggests a protective effect of enrichment factors, pursued during the entire life, in modulating the clinical impact of neurodegeneration. Such an effect should be considered when designing clinical trials.

**References:** 1. Stern, Y., 2009. *Neuropsychologia* 47,2015–2028.; 2. Serra L, Cercignani M, Petrosini L, et al., 2011. *Rejuvenation Res.* Apr;14(2):143-51; 3. Petersen, R., 2004. *J Intern Med* 256:183–194; 4. Scheltens P, Pasquier F, Weerts JG, et al., 1997. *Eur Neurol.*;37(2):95-9; 5. Wahlund LO, Barkhof F, Fazekas F et al.,2001. *Stroke.* Jun;32(6):1318-22.