



## Cognitive reserve and the risk for Alzheimer's disease: a longitudinal study



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### ABSTRACT

This study investigates how cognitive reserve (CR) interacts with neurodegeneration (quantified by medial temporal atrophy, MTA) and macroscopic white matter lesions (WMLs) in delaying the conversion from amnesic mild cognitive impairment to Alzheimer's disease (AD). Forty-two amnesic mild cognitive impairment patients were consecutively recruited. They underwent magnetic resonance imaging and a comprehensive questionnaire to classify them as individuals with low or high CR. Patients were then clinically followed-up for 2 years. The patients' risk for conversion to AD because of CR was estimated by controlling for cognitive efficiency, MTA, and WMLs at baseline. Global cognition was the best predictor of conversion to AD in low CR patients. Conversely, in high CR patients only, WMLs (but not MTA) highly contributed in increasing the risk for conversion to AD. In conclusion, CR interacts with both patients' cognitive features and WMLs in modulating the impact of AD pathology. This seems relevant for clinical prognosis and therapeutic strategies.

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### 1. Introduction

The “cognitive reserve hypothesis” (CR) explains the differences among individuals in their ability to cope with physiological or pathologic cognitive decline (Stern, 2009, 2012). CR has been conceptualized as based on an active model that postulates the existence of compensatory brain mechanisms able to cope with the cerebral damage (Stern, 2009, 2012). An alternative passive model (brain reserve, BR) has also been proposed, which is based on quantifying brain size, neuronal amount, and number of synapses (Stern, 2009, 2012). Both models have been postulated in the past to account for brain resilience to pathologic damage.

Alzheimer's disease (AD), in its most typical presentation, is characterized by memory deficits followed by a progressive increase of cognitive disabilities, until conversion to dementia (Nelson et al., 2009). Accordingly, in AD brains a typical pattern of tissue damage has been identified, with an earlier involvement of the medial temporal lobe structures (Braak and Braak, 1996), followed by a spread of pathology to the lateral temporal, parietal, and frontal cortex (Braak and Braak, 1996). At an individual level, there is no univocal relationship between brain damage and cognitive impairment, and it has been hypothesized that BR and/or CR may modulate the clinical onset of AD (Stern, 2009, 2012). Indeed, because AD results from a progressive accumulation of neuropathologic lesions within a long period of time during which the clinical symptoms are still silent (Elias et al., 2000; Small et al., 2000), it is reasonable to hypothesize that a higher CR and/or BR may contribute in postponing the time point of inflection toward dementia. In fact, participants with a higher CR and/or BR require a more severe extent of AD pathology to manifest symptoms of cognitive decline (Fratiglioni and Wang, 2007; Stern, 2009). We

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recently demonstrated (Serra et al., 2011) in a cross-sectional neuroimaging study that patients at different stages of AD with a higher CR, compared with AD patients with a lower CR, showed more reduced gray matter (GM) volumes in regions typically affected by AD pathology (specifically in the entorhinal cortices and temporal lobes). By contrast, increased GM volume was present in the supramarginal gyrus, posterior cingulate cortex, and precuneus, suggesting that CR modulates selective GM changes that contribute to mitigate the clinical impact of AD (Serra et al., 2011). Other studies support the contention that CR has a protective effect against the clinical occurrence, or at least the detection, of AD (Garibotto et al., 2008; Koepsell et al., 2008; Roe et al., 2008). These studies assessed the relationship between different levels of CR and brain abnormalities involving not only GM but also white matter (WM).

As demonstrated in previous studies based on animal models (Nichol et al., 2009; Petrosini et al., 2009), the development of BR and CR is highly correlated with the extent of environmental enrichment to which the animals are exposed. In the case of humans, we can argue that several cognitive, social, and physical activities can be considered as important factors for developing CR and BR (Stern, 2009, 2012). However, the interaction between CR proxies and abnormalities in the GM and WM still remains unclear.

Aims of the present study were to investigate, for the first time in a longitudinal study, whether different levels of CR: (1) modulate the rate of conversion to AD in patients with amnesic mild cognitive impairment (a-MCI); (2) interact with cognitive functions, contributing to reduce the risk of conversion, and thus postponing the time point of inflection toward dementia; and (3) interact with brain abnormalities to reduce the risk of progression to AD.

Importantly, we decided to use semiquantitative measures of brain abnormalities readily available in clinical settings and not requiring sophisticated and time-consuming image analysis.

## 2. Methods

### 2.1. Participants

A cohort of 42 drug-naïve patients diagnosed as suffering from a-MCI according to current criteria (Petersen et al., 2014) were consecutively recruited in 2010. From a clinical and neuropsychological viewpoint, patients could be classified as follows: (1) patients with amnesic MCI single domain (a-MCI-SD) ( $n = 24$ ), all of them showing an isolated memory deficit; (2) patients with amnesic MCI multiple domain (a-MCI-MD) ( $n = 18$ ), all of them showing memory impairments associated to deficits in at least one more cognitive domain. In particular, patients with a-MCI (either a-MCI-SD or a-MCI-MD) had to report subjective memory impairment at clinical onset, corroborated by an assistant, and confirmed by performances below the normality cutoff scores on at least one of the administered tests for episodic memory (see the following). Patients with a-MCI-SD had to report, as an additional criterion, scores within normal range at neuropsychological tests exploring cognitive functions other than episodic memory. Patients with a-MCI-MD had to report pathologic scores in at least one other cognitive function (i.e., executive function, praxis, and language) in addition to memory. To increase the confidence of recruiting patients genuinely belonging to the AD spectrum, they had to remain stable or worsen at follow-up. None of the patient responded to the diagnostic criteria for dementia (APA, 2000). All patients reported normal scores at the Mini Mental State Examination (MMSE) (Folstein et al., 1975) (Italian normality cutoff score  $\geq 23.8$ ) (Magni et al., 1996). By definition, patients' MCI had to result in very mild or no impact on daily living activities, as confirmed by a total Clinical Dementia Rating score (Hughes et al., 1982) not

exceeding 0.5. Patients with a Hachinski score (Hachinski et al., 1975) higher than 4 were excluded.

All patients had to be right-handed, as assessed by the Edinburgh Handedness Inventory (Büsch et al., 2010), to reduce any potential source of variability because of hemispheric dominance. Major systemic, psychiatric, and other neurologic illnesses were carefully investigated and excluded in all participants. All patients underwent an extensive neuropsychological battery and a questionnaire specifically devoted to assess the level of CR. All participants also underwent a magnetic resonance imaging (MRI) acquisition. Details of these 2 procedures are provided in the following sections. In the present study, we used a longitudinal design following up all patients at 6-month intervals over 24 months. At every follow-up visit, all patients underwent clinical, neuropsychological, and MRI evaluation to reclassify them as stable MCI or AD converters. The diagnosis of AD was in accordance with the clinical criteria established by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). Local ethics committee approval and written informed consent were obtained before study initiation.

### 2.2. Neuropsychological assessment

At both baseline and follow-up, all recruited patients underwent an extensive neuropsychological battery including the following tests: verbal episodic long-term memory: 15-word list (immediate and 15-minutes delayed recall) (Carlesimo et al., 1996); short-term memory: digit span and the corsi block tapping task (Orsini et al., 1987); executive functions: phonological word fluency (Carlesimo et al., 1996) and modified card sorting test (Nocentini et al., 2002); language: naming objects subtest of the BADA ("Batteria per l'Analisi dei Deficit Afasici," Italian for "Battery for the analysis of aphasic deficits") (Miceli et al., 1991); reasoning: Raven Colored Progressive Matrices (Carlesimo et al., 1996); and constructional praxis: copy of simple drawings (Carlesimo et al., 1996). For the purposes of the present study, the scores from all used tests were not adjusted for age and education as these variables were statistically accounted for in the following steps of the analysis. Specifically, we used years and different types of formal education as variables of interest for the computation of CR index, as detailed in the following.

Nine 3-way analyses of variance for repeated measures ( $2 \times 2 \times 2$ ) were used to assess between groups (low and high CR level) by cognitive status (converters and nonconverters) by time (baseline and follow-up) differences. To avoid the type-I error Bonferroni correction was applied ( $p$ -value threshold for significance was computed as  $\alpha = 0.05/9 = 0.005$ ).

#### 2.2.1. Proxies of cognitive reserve

All participants were administered a questionnaire to assess the activities which are likely to impact on cognitive reserve and practiced by them during 2 age spans: before their 40s and between their 40s and 65 years of age. These include the level of education (measured by the number of years at school and university attendance), the type of school and the university degree obtained, the main occupation (quantifying the type of job and the number of years spent in it), and the type and/or frequency of leisure activities, including both cognitive activities (reading, writing, playing instruments, and so forth), social activities (charity work, entertaining friends, looking after a pet, and so forth), and physical activities (sports, walking, climbing, house work, knitting, and so forth). Participants had to report the frequency of engagement in these activities, choosing between 5 possible answers, ranging from "daily" to "never." The questionnaire included 8 entries for

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