Education Modulates the Impact of White Matter Lesions on the Risk of Mild Cognitive Impairment and Dementia

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Objectives: *Conflicting results have been reported regarding the association between white matter lesions (WML) and cognitive impairment. We hypothesized that education, a marker of cognitive reserve (CR), could modulate the effects of WML on the risk of mild cognitive impairment (MCI) or dementia.* **Methods:** *We followed 500 healthy subjects from a cohort of community-dwelling persons aged 65 years and over (ESPRIT Project). At baseline, WML volume was measured using a semi-automatic method on T2-weighted MRI. Standardized cognitive and neurological evaluations were repeated after 2, 4, and 7 years. The sample was dichotomized according to education level into low (≤8 years) and high (>8 years) education groups. Cox proportional hazard models were constructed to study the association between WML and risk of MCI/dementia.* **Results:** *The interaction between education level and WML volume reached significance ($p = 0.017$). After adjustment for potential confounders, the association between severe WML and increased MCI/dementia risk was significant in the low education group (≤8 years) ($p = 0.02$, hazard ratio [HR]: 3.77 [1.29−10.99]), but not in the high education group (>8 years) ($p = 0.82$, HR: 1.07 [0.61−1.87]).* **Conclusions:** *Severe WML significantly increases the risk of developing MCI/dementia over a 7-year period in low educated participants. Subjects with higher education levels were seen to be more likely to be*

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resilient to the deleterious effects of severe WML. The CR hypothesis suggests several avenues for dementia prevention. (Am J Geriatr Psychiatry 2013; ■:■−■)

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Cerebral white matter lesions (WMLs) are commonly found on magnetic resonance imaging (MRI) scans of elderly people. WMLs are thought to be the result of degenerative changes in small vessels,[1,2] and hypertension and arteriosclerosis are considered significant risk factors.[3,4] Although several studies indicate that WMLs are associated with cognitive decline and incident dementia,[5] others suggest no relationship between WMLs and cognition.[6,7] The relationship of WMLs to cognitive impairment in normal aging and dementia is still not fully understood. Discrepant findings may be due in part to the heterogeneity of the cognitive domains assessed, differences in MRI methodologies, and variability in the cognitive status of the subjects. Apart from differences in study design, there is also considerable variability in the density of WMLs in normal older adults, and the relationship of density to cognitive dysfunction: people may differ in their capacity to compensate for the deleterious effect of cerebral lesions, as has already been observed for some people with extensive Alzheimer disease (AD) pathology (senile plaques and neurofibrillary tangles) who do not exhibit cognitive impairment.[8] Identifying factors associated with the ability to tolerate WML accumulation has important implications for promoting successful cognitive aging.

A concept that has been developed to explain how neurodegenerative changes that are similar in nature and extent may give rise to considerable variation in terms of cognitive consequences is termed the "cognitive reserve," which could be active or passive.[9] This may be defined as an individual's ability to make flexible and efficient use of available neuronal networks in the active model,[10] and as the capacity of the brain itself to cope with pathology better than others in the passive model. The reserve hypothesis has been evoked in relation to many brain disorders, notably those that are aging-related, but also to head injury, schizophrenia, depression, and multiple sclerosis.[11] Patients with AD or mild cognitive impairment (MCI) with higher cognitive reserve (CR) showed an increased capacity to cope with reduced white matter integrity in diffusion tensor imaging studies compared with patients with lower CR.[12,13] Although one study did not find direct evidence to support the CR hypothesis,[14] several others volumetric MRI studies observed that CR could influence the relationship between WML and some cognitive domains[14−20] and dementia.[21] CR could indeed balance the negative impact of pathological brain burden such as that of WMLs on late-life cognitive ability in people without cognitive impairment acting through both protective and compensatory mechanisms. The most frequently used proxies for CR have been education, occupational attainment, premorbid intelligence quotient, head size, and mentally stimulating activities.[22−25] The only study to date investigating the influence of CR on the relationship between WMLs and dementia was cross-sectional,[21] and used head size as a proxy for CR, which is assumed to reflect the passive model. Moreover, WMLs were estimated with computed tomography scans, which are less sensitive than MRI in detecting WMLs. To our knowledge, education, a proxy of the active model of CR, has not been considered as a possible moderating factor in the association between WML load and onset of dementia or MCI; outcomes that reflect a global cognitive disorder covering several cognitive domains.

We thus examined in a 7-year longitudinal population-based study whether education level could modulate the impact of WMLs on risk of MCI/dementia in cognitively nonimpaired elderly persons.

METHODS

Study Population

Between 1999 and 2001, 1,863 people aged 65 years and older were recruited from the electoral rolls for the ESPRIT Project (Montpellier, France). The study design has been described elsewhere.[26] The study protocol was approved by the ethics committee of the University Hospital of Bicêtre (France) and written informed consent was obtained from each participant. Examinations comprised a standardized