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Impact of cognitive reserve on clinical and neuropsychological measures in patients with mild cognitive impairment

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Abstract

Objective: Cognitive reserve influences age of onset, speed of progression, and clinical manifestations of Alzheimer's disease. We investigated whether cognitive reserve interacts with clinical and neuropsychological parameters in mild cognitive impairment (MCI).

Methods: In this cross-sectional study, we recruited 273 people (70.6 ± 10.1 years, 54.6% women) suffering from subjective memory complaints (n = 65), MCI (n = 121), or dementia (n = 87). Patients underwent neuropsychological evaluation, laboratory testing, and brain imaging. Additionally, we obtained information on years of education and help-seeking motivation.

Results: MCI patients with a university degree were significantly older than those without (71.6 ± 9.6 vs. 66.9 ± 10.3, p = 0.02). University-educated MCI patients demonstrated superior performance in verbal fluency. Intrinsic help-seeking motivation (self-referral) was associated with higher cognitive reserve. Female MCI patients presented with greater intrinsic motivation.

Conclusion: Cognitive reserve modulates clinical and neuropsychological measures in patients with MCI.

Keywords: cognitive reserve, intelligence, educational attainment, mild cognitive impairment, dementia

Cognitive reserve is a theoretical construct used to explain differences in sustaining cognitive function within normal aging and neurodegenerative disease.[1] Regarding its neural correlates, functional MRI data imply network effects. Resilience of neuronal networks, efficient network recruitment, and higher global connectivity of the frontal cortex mediate the effects.[2–4] Cognitive reserve comprises several parameters related to education and lifetime experiences measurable by different proxy variables.[5] Factors that influence cognitive reserve include the years of formal education, educational and occupational attainment, intelligence, level of engagement in cognitively stimulating activities, socioeconomic status, and early life experiences.[5] However, these factors show complex and overlapping relationships. There are, for example, genetic influences on intelligence, but also potentially bidirectional relations to socioeconomic status and education.[6] The years spent in formal education are often used to assess cognitive reserve, although the duration of education represents a static variable not capturing aspects, such as quality

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of learning and individual differences in continuous engagement.[5] Furthermore, different components of cognitive reserve may vary in their influence during the life span, which also limits how proxy variables reflect cognitive reserve.

A lack of stimulating cognitive activities and physical inactivity are among the most relevant modifiable risk factors for dementia, making cognitive reserve a promising intervention target.[1] In line with the cognitive reserve hypothesis, studies consistently show a lower risk of mild cognitive impairment (MCI) and dementia in higher educated subjects.[7–9] The protective potential of cognitive reserve against early manifestations of Alzheimer's disease has been verified in longitudinal studies. Soldan and colleagues operationalized cognitive reserve with a composite score of reading vocabulary and years of education, and demonstrated an influence on symptom onset in MCI patients, which was independent from medial temporal lobe atrophy and genetic risk.[10] Others showed lower MCI conversion rates in subjects with subjective cognitive decline and higher intellectual activities.[11] A further longitudinal study illustrated that a higher cognitive reserve delays the conversion from subjective cognitive decline to MCI up to 9 years.[12]

In individuals with a high cognitive reserve, cognitive decline manifests at a pathologically more advanced stage because social, cognitive, and physical activities could mask early clinical symptoms. Once these become obvious, advanced neuropathology contributes to a more rapid clinical progression.[4,13]

We investigate the influence of cognitive reserve on clinical and neuropsychological parameters in patients with MCI. Cognitive reserve effects and executive functions are both mediated by a broad network of multiple brain structures,[14] less dependent upon focal, for example medial temporal, brain damage. Therefore, we hypothesized that MCI patients with higher cognitive reserve show less impairment in executive functioning. Assessing help-seeking motivation should complement cognitive evaluation.[15] Since knowledge of Alzheimer's disease and the perception of one's own cognitive performance contribute to dementia worries,[16] we also hypothesized that cognitive reserve is associated with greater help-seeking motivation among MCI patients.

Design and methods

Participants and procedures

We recruited 273 people (70.6 ± 10.1 years; 54.6% women) from January 2016 until December 2018 through our memory clinic (university hospital, outpatient service). These individuals suffered from subjective memory complaints (SMI),[17] MCI (Petersen criteria, 1.0 standard deviation criterion,[18,19]), or dementia (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria[20]). We obtained written informed consent; our university's ethics committee approved the study. Participants underwent medical and neurocognitive evaluation, laboratory testing, and brain imaging. In the psychometric tests, we investigated intelligence (Horn's LPS reasoning test (the German Leistungs-Prüf-System; LPS,[21]), Multiple Choice Word Test-B (MWT-B,[22])); memory (Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list recall, Wechsler Memory Scale (WMS) digit span backward, Nuremberg Age-Inventory (NAI)); verbal fluency (CERAD verbal fluency test); and executive function/attention (trail making test). For the interpretation of test results we used age-corrected z-scores. In addition, we obtained information on years of education, educational achievements, and help-seeking motivation (Table 1). Different help-seeking motivation was reflected by intrinsic help-seeking motivation (self-referral) or extrinsic help-seeking motivation (referral by others) regarding presentation to our memory clinic. Intrinsic help-seeking motivation was defined as the individual's own decision to make an appointment (either directly or after asking others for advice). The presentation was defined as extrinsic help-seeking motivation when others recommended the appointment without prior indication that the person would find it necessary. The way of referral was explored by the physician at a patient's first presentation.

Statistical analyses

For the description of sociodemographic and clinical data, we constructed cross tables and calculated mean values, standard deviations, and frequencies. Depending on data level analyses, we conducted *t*-tests, univariate analysis of variance (ANOVA), multivariate analysis of variance (MANOVA), and logistic regression. Age and sex were included as covariates where appropriate. Regarding multiple comparisons, *p* values were adjusted according to Bonferroni. Statistical computations were conducted using IBM SPSS statistics for Windows, version 25.

Demographic characteristics

In our sample, 121 patients were diagnosed with MCI, 87 with dementia, and 65 with SMI. Thirty seven percent of the patients graduated from university; the remaining individuals reported a professional education (graduation from school and subsequent non-academic apprenticeship) or solely graduated from school. We operationalized a university degree as reflecting "high" and no university degree as reflecting "low" cognitive reserve. Further demographic characteristics are illustrated in Table 1.

Results

Although cognitive reserve comprises different factors, formal education can be used as a reliable proxy measure.[23] On investigating the influence of cognitive reserve on the

Table 1. Demographic characteristics and clinical parameters across diagnostic group

		n (%)	Mean (SD)	Range
Age		273 (100%)	70.6 (10.1)	50 (44–94)
Sex	Men	124 (45.4%)		
	Women	149 (54.6%)		
Educational achievement	School	10 (3.7%)		
	Professional education	162 (59.3%)		
	University	101 (37.0%)		
University education	SMI	32 (49.2%)		
	MCI	38 (31.4%)		
	Dementia	31 (35.6%)		
Education years		273 (100%)	13.7 (2.9)	18 (6–24)
Diagnosis	SMI	65 (23.8%)		
	MCI	121 (44.3%)		
	Dementia	87 (31.9%)		
Help-seeking motivation (self-referral)		162/269 (60.2%)		
	SMI	53/65 (81.5%)		
	MCI	81/117 (69.2%)		
	Dementia	28/87 (32.2%)		

SMI = subjective memory impairment; MCI = mild cognitive impairment.

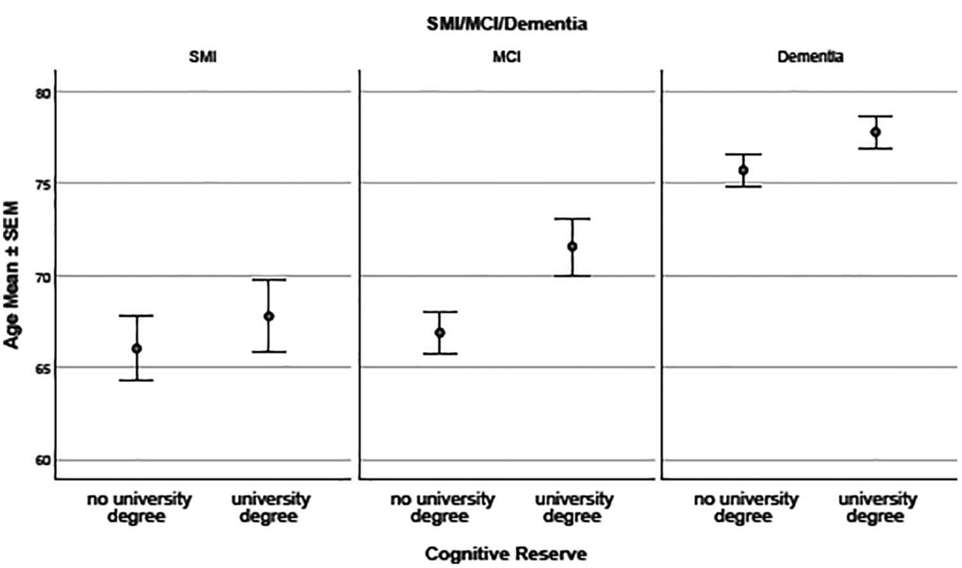

Figure 1. Age at time of diagnosis depending on cognitive reserve in the diagnostic groups.

age of disease onset, we found that patients with MCI and a university degree were older compared with MCI patients without university education (71.6 ± 9.6 vs. 66.9 ± 10.3; $p = 0.02$). We did not find this effect in subjects with SMI (66.0 ± 10.2 vs. 67.78 ± 11.0; $p = 0.51$) or dementia (75.7 ± 6.8 vs. 77.8 ± 4.9; $p = 0.14$) (Figure 1). We further investigated whether help-seeking motivation depends on cognitive reserve. Logistic regression including all diagnostic groups using age and sex as covariates demonstrated that intrinsic help-seeking motivation was associated with younger age (B = 0.081; Exp(B) = 1.085; 95% CI [1.05, 1.12]; SE = 0.02; $p < 0.001$), female sex (B = 0.679; Exp(B) = 1.972; 95% CI [1.11, 3.50]; SE = 0.29; $p = 0.02$), and higher cognitive

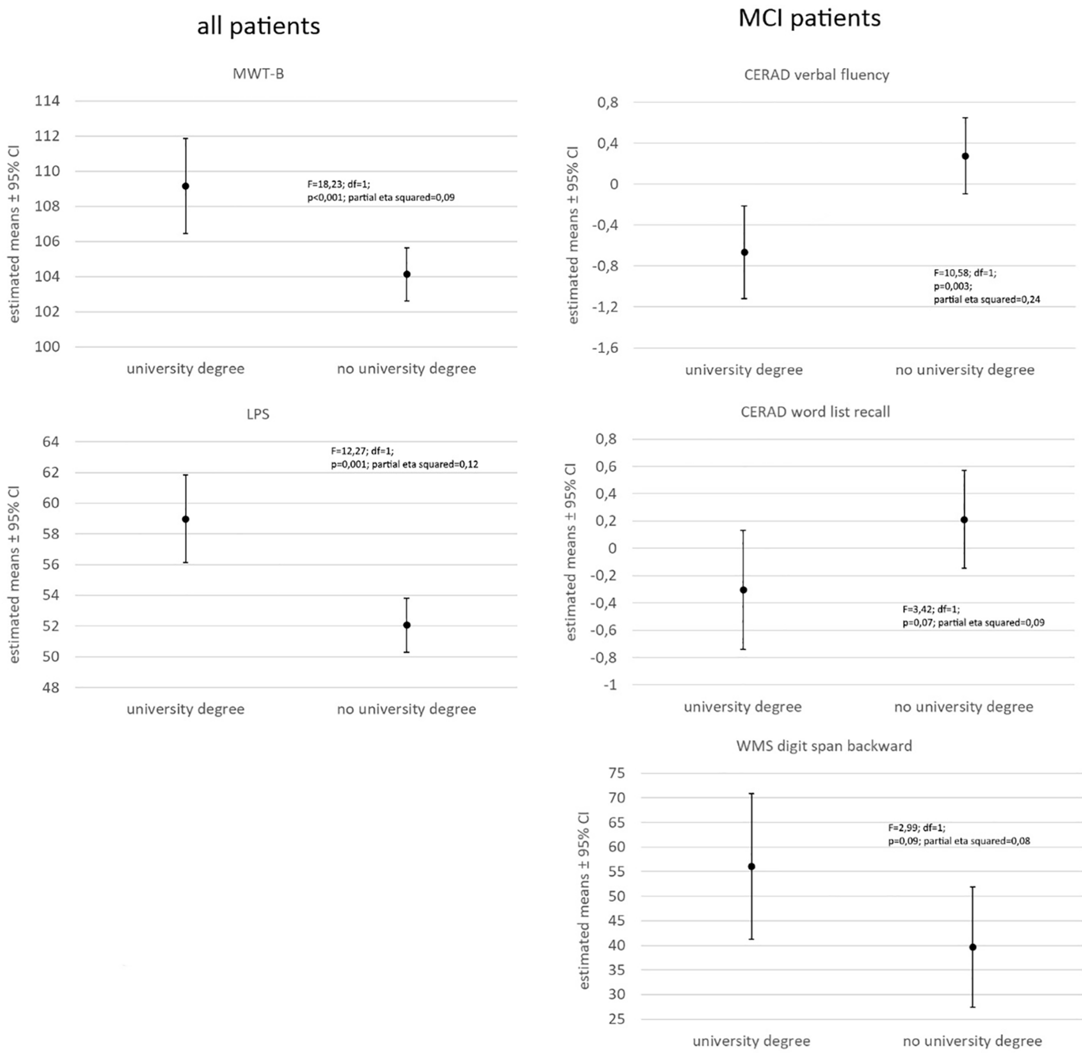

Figure 2. Cognitive reserve modulates neurocognitive test performance.

reserve (B = 0.765; Exp(B) = 2.150; 95% CI [1.17, 3.95]; SE = 0.31; p = 0.01). We did not find this association when analyzing SMI or dementia patients separately. Among patients with MCI, compare to men, women presented with greater intrinsic motivation (B = 1.058; Exp(B) = 2.88; 95% CI [1.21, 6.84]; SE = 0.44; p = 0.02).

The influence of cognitive reserve on neurocognitive test scores is visualized in Figure 2.

Discussion and implications

We found an association of higher cognitive reserve with the age at the time of diagnosis in patients with MCI but not in subjects with SMI or dementia. The achievement of higher neuropsychological test scores associated with university education was also only detectable in subjects with MCI. These data suggest a slower cognitive decline and a more advanced age at presentation in higher educated patients with MCI. However, in our cross-sectional study, we did not have premorbid neuropsychological data; therefore future longitudinal investigations would be helpful to differentiate the temporal influence of cognitive reserve in normal and pathological aging. These findings are in line with previous data showing a protective potential of higher cognitive reserve in MCI,[7–9] but limited impact in later disease stages.[13] Furthermore, accelerated cognitive decline in higher educated patients with dementia due to advanced brain pathology at symptom onset needs to be considered,[4] possibly reflecting a failure of cognitive reserve-associated mechanisms compensating for advanced neuropathology. Delayed manifestation of MCI may therefore not compensate for a more pronounced though not necessarily linear cognitive decline in patients with a high cognitive reserve.[24] Etiologic heterogeneity may also contribute to the negative finding in the SMI group. Furthermore, the awareness for changes in cognition could be relatively independent of cognitive reserve in SMI patients. We demonstrate that higher-educated patients with MCI show greater intrinsic help-seeking motivation when compared with lower-educated MCI patients. Dementia-related knowledge as well as frequent engagement in intellectual activities with higher cognitive demand might contribute to earlier recognition of impairment. Our results imply that cognitive reserve shows associations with intrinsic help-seeking motivation. Clinicians should appreciate possible differences in awareness for cognitive changes, but also consider that MCI manifests at a later pathological stage in people with a longer educational history.

Cognitive reserve is mediated by efficient neural network recruitment and a higher global connectivity.[2–4] We found a positive association of verbal fluency and cognitive reserve in MCI patients. Additional trends for comparable associations in word list recall and the digit span backward test further characterize this finding. In Alzheimer's disease, verbal fluency impairment correlates with disease progression.[25] We show that verbal fluency tests are affected by different levels of cognitive reserve in patients with dementia and with MCI. These findings should be reproduced in larger samples.

We conclude that in patients with MCI, cognitive reserve modulates the age at time of diagnosis, help-seeking motivation, and neuropsychological test results. This underlines the significance of appreciating aspects of cognitive reserve in the clinical evaluation of MCI.

Disclosure

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