



Different MMSE domains are associated to cognitive decline and education

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ABSTRACT

The Mini-Mental State Examination (MMSE) is a long-established test to screen for dementia, estimate the severity and monitor the progression of cognitive impairment. The MMSE total score is dependent upon demographic factors, particularly education, but little is known about how education influences the 6 distinct MMSE cognitive domains. The present study aims to understand how the performances in the MMSE cognitive domains reflect clinical diagnosis and educational level. The study recruited 1043 participants, comprising 388 healthy controls, 360 patients with Mild Cognitive Impairment (MCI) and 295 patients with dementia. The association of the MMSE cognitive domains scores with clinical diagnosis (healthy, MCI, dementia) and educational level (primary education, middle school, high school and university/college) was analyzed with a multivariate ordinal regression model. The scores in all MMSE domains were generally higher in healthy controls as compared to patients with MCI, and higher in these as compared to patients with dementia. The MMSE domain *Constructional ability* was associated to the education level, the domains *Orientation*, *Recall* and *Language* were associated to diagnosis, *Attention and calculation* was associated to both education level and diagnosis, and *Registration* was not associated to either education or diagnosis. In conclusion, impairment in specific MMSE domains pinpoints cognitive decline, probably indicating brain areas affected by neurodegeneration, and impairment in others reflects lower education levels and the lack of acquisition of relevant schooling abilities.

KEYWORDS

cognitive decline; dementia; domains; education; Mini-Mental State Examination; MMSE; Mild Cognitive Impairment

Introduction

The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) is a long-established test to screen for dementia, in both clinical and epidemiological case finding contexts, and is also widely used to estimate the severity and to monitor the progression of cognitive impairment (Moscello & Boncinelli, 2006). The role of MMSE as a single test to identify early stages of cognitive decline, like Mild Cognitive Impairment (MCI), is however limited (Arevalo-Rodriguez et al., 2021).

Performance in the MMSE reflects cognitive impairment, but is also dependent upon demographic factors, namely age, education and cultural background (see review by Tombaugh & McIntyre, 1992). Several studies found that education is the most important demographic factor influencing the MMSE score (O'Connor et al., 1989; Uhlmann & Larson, 1991; Guerreiro et al., 1994; Bertolucci et al., 1994; Morgado et al., 2010). The influence of education on MMSE performance was confirmed across diverse backgrounds. Thus, Murden et al. (1991) and Matallana et al. (2011) observed that the MMSE is affected by education and Teresi et al. (1995) found that specific items in MMSE show an education bias, when studying educationally and ethnically diverse populations.

Accordingly, several authors proposed the use of MMSE cutoff values adjusted for the education level (Uhlmann & Larson, 1991; Schmand et al., 1995), or adding a bonus point to the MMSE score of less educated people (Khater & Abouelezz, 2011).

The MMSE comprises 6 different main subtests, namely *Orientation to time and place*, *Registration*, *Attention and calculation*, *Recall*, *Language* and *Constructional ability*, which are generally named cognitive domains, although some subtests may not show sufficient divergent validity to warrant a conclusion of their domain specificity (Tierney et al., 1997).

Certain cognitive domains are more sensitive, and others more resilient, to cognitive impairment, thus specific MMSE items decay at different points with disease progression (Ashford et al., 1989). Temporal *Orientation* items and *Recall* decline early in the course of the disease (Ashford et al., 1989) and can discriminate normal controls from patients with mild Alzheimer's disease (AD) (Fillenbaum et al., 1994). Furthermore, a lower score in orientation to time is associated with future cognitive decline (Guerrero-Berroa et al., 2009).

Less is known about how the performance in different MMSE cognitive domains is influenced by the educational level. A previous study found that more educated people performed better in *Attention and calculation*, some

Language items and *Constructional ability* (Jones & Gallo, 2002). Similarly, in another study, more educated people had better performances in *Orientation to time and place*, *Attention and calculation*, some *Language* items and *Constructional ability* (Laks et al., 2010). Both studies were performed in healthy people.

The present study has the advantage of evaluating how the performances in distinct MMSE cognitive domains reflect both clinical diagnosis (healthy, MCI, dementia) and educational level (primary education, middle school, high school and university/college), thus taking into account possible interactions between diagnosis and education. From the evidence reviewed above, we might expect that the pathological process of neurodegeneration and the lack of acquisition of schooling abilities might hinder different MMSE cognitive domains. On the other hand, it could be that some MMSE domains might generally be harder and more demanding for both cognitively impaired and less educated people. We thus hypothesize that 1) Some specific MMSE domains decline along the disorder process, from healthy participants to patients with MCI and to patients with dementia, 2) Some specific MMSE domains are affected in less educated participants, 3) Other MMSE domains might be related to both diagnosis and education.

Methods

Study type

This is an observational cross-sectional study.

Participants

Both participants with MCI and dementia were patients with cognitive complaints recruited at a memory clinic in Lisbon from 2010 to 2020. Controls were volunteers attending in the same period a health itinerant unit that aims to screen and promote general health, a blood donor center, a leisure center for retired people, and a senior citizens college and university, all in the area of Lisbon. A total of 1034 adults participated in the study. Participants consisted of 388 healthy controls, 360 patients with MCI and 295 patients with dementia, 67% of whom were diagnosed with AD.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee, all participants gave their written informed consent.

Inclusion criteria

Participants with dementia fulfilled the DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000).

Diagnosis of amnesic MCI was adapted from Petersen et al., 1999: (1) Memory complaints present at the clinical interview. (2) Abnormal memory function, documented by a cutoff of the Logical Memory test delayed recall score below -1.0 SD the norms for age and education. These so-called

liberal criteria according to Jak et al., 2009 were adopted to prevent the exclusion of participants that from a clinical point of view suffered from MCI (Busse et al., 2006; Ribeiro et al., 2007). (3) Absence of major repercussions on daily life (the patient may report difficulties concerning complex day-to-day activities).

Control participants had: (1) No memory complaints. (2) Normal memory function, documented by a cutoff of the Logical Memory test delayed recall score above -1.0 SD the norms for age and education. (3) Normal activities of daily life.

As inclusion criteria for all groups, participants were: (1) Native Portuguese speakers. (2) ≥ 50 years old. (3) Education level ≥ 1 years.

Exclusion criteria

(1) Neurological disorders (stroke, tumors, significant head trauma, and epilepsy), psychiatric conditions (including major depression), or uncontrolled medical illness (hypertension, metabolic, endocrine, toxic, and infectious diseases) able to interfere with cognition. (2) Psychoactive medications with possible influence on cognition. (3) Chronic alcohol or drug abuse. (4) Sensory deficits likely to interfere with assessment.

Measures

All neuropsychological assessments were carried out by the same team of trained neuropsychologists in a quiet room and comprised:

1. Battery of Lisbon for the Assessment of Dementia (BLAD; Garcia, 1984). The BLAD is a comprehensive neuropsychological battery that includes some tests from the Wechsler Memory Scale (Wechsler, 1945) and is validated for the Portuguese population. For this study the Logical Memory test (immediate and delayed free recall) was considered.
2. Geriatric Depression Scale (GDS; Yesavage et al., 1982). The GDS is a self-report assessment used specifically to identify depression in the elderly. For this study a short form (15 items) of the self-report instrument was used. The Portuguese version was applied (Barreto et al., 2008).
3. Subjective Memory Complaints (SMC) scale (Schmand et al., 1996). This scale comprises 10 individual items concerning difficulties in daily life memory tasks. Total scores range from 0 (absence of complaints) to 21 (maximum complaints score). The Portuguese version was applied (Ginó et al., 2008).
4. The main neuropsychological instrument of interest in the present study was the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The Portuguese version was applied (Guerreiro et al., 1994). It comprises 6 main cognitive domains, namely *Orientation to time and place* (10 points), *Registration* (3 points), *Attention and calculation* (5 points), *Recall*

(3 points), *Language* (8 points) and *Constructional ability* (1 point), thus the total scores range from 0 to 30 (maximum cognitive score).

Statistical analysis

Comparisons of demographic, clinical and neuropsychological characteristics among healthy controls, patients with MCI and patients with dementia, were done with the non-parametric Kruskal-Wallis test followed by Dunn's *post hoc* test corrected by the Bonferroni method, since most variables did not follow a normal distribution. Comparisons of categorical variables were performed with the Pearson χ^2 test. The Statistical Package for the Social Sciences (SPSS version 24; SPSS Inc, Chicago, Ill., USA) was used.

Data from the neuropsychological assessment were standardized according to the age and education norms from the Portuguese population (Guerreiro, 1998) and *z* scores were calculated according to the equation $z = (x - \text{mean}) / \text{SD}$.

Regarding education, 4 education levels were considered, according to the number of school years successfully completed: 1–4 years (primary education), 5–9 years (middle school), 10–12 years (high school) and more than 12 years of education (university/college), these categories correspond to the traditional Portuguese educational system (Freitas et al., 2015).

To evaluate the effects of MMSE cognitive domains on education and diagnosis, a multivariate ordinal regression model was done, using the R package *mvord* and the multiple measurement object *MMO2* (Hirk et al., 2020; Package 'mvord', 2020). Noteworthy, the use of the ordinal regression model was not intended to support causal inferences, but rather to model the relationship between ordinal education level, clinical diagnosis and MMSE domains quantitative scores. The 6 MMSE cognitive domains (*Orientation*, *Registration*, *Attention and calculation*, *Recall*, *Language*, *Constructional ability*) were considered independent variables. Variables able to influence the performance in the MMSE, namely age and GDS, were added as independent variables to the multivariate ordinal regression model. Clinical diagnosis (healthy, MCI, dementia) and educational level (primary education, middle school, high school and university/college) were dependent ordinal variables. The link function logit was chosen since the classes of the dependent variables were uniformly distributed (Marôco, 2014). *Post hoc* univariate ordinal regression analyses were performed to find out the differences in classes of clinical diagnosis and educational level that were responsible for the observed associations with the MMSE cognitive domains. For this purpose, statistically significant differences in the thresholds were determined. Values of $p < 0.05$ were considered statistically significant and p values < 0.001 were considered highly statistically significant.

Results

Demographic and clinical characteristics are shown in Table 1. Patients with dementia were older, as might be expected

from a more advanced stage of the disease. Performance in Logical Memory was higher in healthy controls as compared to patients with MCI, and higher in these as compared to patients with dementia. Both patients with MCI and with dementia had more depressive symptoms and subjective memory complaints as compared to healthy controls.

The scores for the 6 MMSE domains as well as the total MMSE score are shown in Table 2. The scores in all MMSE domains were generally higher in healthy controls as compared to patients with MCI, and higher in these as compared to patients with dementia.

The association of the MMSE cognitive domains with clinical diagnosis and educational level was analyzed with a multivariate ordinal regression model. Since age is known to generally influence the performance in the MMSE, and since we observed significant negative correlations between almost all MMSE subscores and the GDS score, age and the GDS score were added as independent variables to the multivariate ordinal regression model (Table 3). One MMSE domain was positively associated to the education level - *Constructional ability*, that is, more educated participants were able to copy the intersecting pentagons correctly. Three MMSE domains were negatively associated to the diagnosis - *Orientation*, *Recall*, *Language*, that is, the scores in these domains declined when moving from healthy to MCI and to dementia participants. One MMSE domain was associated to both education level and diagnosis - *Attention and calculation*, the scores in this counting backwards task were higher for more educated participants and declined along clinical progression. Finally, *Registration*, that is, the ability to repeat the 3 words immediately after they were heard, seemed a relatively undemanding task for both cognitively impaired and less educated people.

Discussion

The main finding of the present study is that performances in distinct MMSE domains were differentially associated to clinical diagnosis and educational level.

Constructional ability, that is, the capability to copy two intersecting pentagons, was positively associated with the education level. This test is recognized as quite difficult for poorly literate or illiterate populations (Raina et al., 2015; Pellicer-Espinosa & Díaz-Orueta, 2021). Previous studies performed in healthy people consistently found that more educated people had better performances in the MMSE domain *Constructional ability* (Jones & Gallo, 2002; Laks et al., 2010).

Memory deficits are the initial and more prominent cognitive deficits in Alzheimer's disease, the most frequent etiology of MCI and dementia, reflecting the typical hippocampal atrophy observed in the course of the disease (Dubois et al., 2007). Temporal *Orientation* items and *Recall* are affected early in the course of the disease (Ashford et al., 1989; Fillenbaum et al., 1994). The present observations that the MMSE memory related domains *Orientation* and *Recall* are associated to the diagnosis were thus expected. The present study found that *Language* is also associated to the

Table 1. Demographic and clinical characteristics.

	Control n = 388	MCI n = 360	Dementia n = 295	Statistical significance
Age at assessment, years, mean (SD) [min-max]	70.8 (7.3) [50-89]	71.9 (6.9) [50-88]	76.1 (7.6) [51-95]	Dementia > MCI, Control*
Gender, n, female/male (% female)	243/145 (62.6%)	202/158 (56.1%)	149/146 (50.5%)	Not significant [#]
Education, years, mean (SD)	8.8 (4.7)	8.8 (4.3)	8.2 (4.6)	Not significant*
Primary, n (%)	149 (38.4%)	116 (32.2%)	124 (42%)	
Middle, n (%)	89 (22.9%)	115 (31.9%)	74 (25.1%)	
High, n (%)	59 (15.2%)	52 (14.4%)	38 (12.9%)	
University, n (%)	91 (23.5%)	77 (21.4%)	59 (20%)	
Logical Memory test - Immediate Recall, z-score (SD)	0.20 (1.16)	-1.97 (0.82)	-2.56 (0.78)	Control > MCI > Dementia*
Logical Memory test - Delayed Free Recall, z-score (SD)	0.81 (0.99)	-1.80 (0.76)	-2.09 (0.68)	Control > MCI > Dementia*
Geriatric Depression Scale - GDS, mean (SD)	2.72 (2.61)	4.37 (3.24)	4.52 (3.28)	Dementia, MCI > Control*
Subjective Memory Complaints - SMC, mean (SD)	5.31 (2.96)	9.11 (4.25)	8.33 (4.00)	Dementia, MCI > Control*

*Kruskal-Wallis test followed by post hoc Bonferroni test.

[#]Pearson χ^2 test.

diagnosis, language capabilities are also affected early in the course of the disease (Ribeiro et al., 2006; Cardoso et al., 2014).

Attention and calculation was the only MMSE domain associated to both diagnosis and education level. In this task, the participant is asked to count backwards. In the original version, begin with 100 and counting backwards by 7s, stopping after 5 subtractions. This test is considered difficult for people with low literacy (Rosselli et al., 2006; Pellicer-Espinosa & Díaz-Orueta, 2021), as a matter of fact in the Portuguese adaptation of the MMSE a simplified version beginning with 30 and counting backwards by 3s substituted for the original version that many people would not be able to accomplish (Guerreiro et al., 1994). Performance in the MMSE domain *Attention and calculation* was previously found to be hindered in less educated healthy people (Jones & Gallo, 2002; Laks et al., 2010), and show early loss in disease progression (Ashford et al., 1989), in accordance to the present study.

Among the different demographic factors that influence the total MMSE scores (see review by Tombaugh & McIntyre, 1992), education appears to be most important (O'Connor et al., 1989; Uhlmann & Larson, 1991; Guerreiro et al., 1994; Bertolucci et al., 1994; Morgado et al., 2010). Accordingly, in the present study the addition of age and GDS to the statistical model did not modify the main results. Noteworthy, we did not include illiterate people in the present study for two reasons. The first is that illiterate people are becoming infrequent in the general population due to the educational progress in the society. The second reason is that illiterate people are not able to perform several cognitive items in MMSE, requiring the need to establish very low cutoff scores in this population (Guerreiro et al., 1994).

To reduce the time of application, several shorter versions of the MMSE have been developed (Roccaforte et al., 1992; Callahan et al. (2002); Schultz-Larsen et al., 2007). In practical terms, the domains that are both sensitive to cognitive decline and resistant to education differences might be particularly adequate for selection of the MMSE domains to keep in shorter versions. Accordingly, the items of *Temporal Orientation* and *Recall* were selected for the shorter version of the MMSE proposed by Callahan et al., 2002. In the same line, following a Rasch item analysis, the items of *Temporal orientation*, *Registration*, *Recall*, an item from *Language*, and *Constructional ability* were selected for the shorter version of the MMSE proposed by Schultz-Larsen in 2007.

The main limitation of the present study is its cross-sectional design, future studies would follow up the decay in the distinct MMSE cognitive domains along the trajectory of cognitive decline, from healthy status to MCI and to dementia, taking into account the education level. It should be recognized that mild to moderate patients with dementia were included, with an average MMSE of 19.8 points, and the findings may not be applicable to advanced stages of the disease. Furthermore, due to the biologically heterogeneous nature of our sample (about two thirds of patients with AD, and one third with other dementing disorders),

Table 2. MMSE scores.

MMSE Domains	Control <i>n</i> = 388	MCI <i>n</i> = 360	Dementia <i>n</i> = 295	Statistical significance *
Orientation Total, mean (SD)	9.91 (0.38)	8.50 (1.67)	5.85 (2.05)	Control > MCI > Dementia
Temporal, mean (SD)	4.92 (0.36)	3.96 (1.26)	2.03 (1.55)	Control > MCI > Dementia
Spatial, mean (SD)	4.98 (0.12)	4.54 (0.67)	3.84 (0.93)	Control > MCI > Dementia
Registration, mean (SD)	2.99 (0.88)	3.00 (0.53)	2.94 (0.35)	Control, MCI > Dementia
Attention and calculation, mean (SD)	4.68 (0.72)	4.52 (0.91)	3.24 (1.78)	Control, MCI > Dementia
Recall, mean (SD)	2.46 (0.72)	1.11 (1.09)	0.40 (0.75)	Control > MCI > Dementia
Language, mean (SD)	7.92 (0.29)	7.67 (0.65)	6.91 (1.21)	Control > MCI > Dementia
Constructional ability, mean (SD)	0.77 (0.42)	0.75 (0.43)	0.40 (0.49)	Control, MCI > Dementia
MMSE Total	28.7 (1.4)	25.5 (2.9)	19.8 (4.2)	Control > MCI > Dementia

*Kruskal-Wallis test followed by Dunn's post hoc test with Bonferroni correction.

Table 3. Association of the MMSE cognitive domains scores, age and GDS with clinical diagnosis and educational level.

	Clinical diagnosis				Education level			
	regression coefficient	SE	z value	<i>p</i>	regression coefficient	SE	z value	<i>p</i>
Intercept	16.651	3.023	5.507	<0.001	1.907	1.493	1.278	NS
Age	0.004	0.010	0.451	NS	-0.044	0.008	-5.424	<0.001
GDS	0.109	0.024	4.537	<0.001	-0.122	0.019	-6.362	<0.001
Orientation	-0.741	0.053	-14.028	<0.001	-0.075	0.039	-1.925	NS
Registration	-0.389	0.922	-0.423	NS	0.139	0.425	0.327	NS
Attention and calculation	-0.188	0.075	-2.499	<0.01	0.301	0.063	4.771	<0.001
Recall	-0.869	0.086	-10.109	<0.001	-0.074	0.061	-1.205	NS
Language	-0.835	0.115	-7.242	<0.001	0.100	0.071	1.405	NS
Constructional ability	-0.149	0.167	-0.890	NS	0.880	0.142	6.188	<0.001

The parameters of the multivariate ordinal regression model are shown; GDS, Geriatric Depression Scale; SE, standard error; statistically significant values are shown in bold.

extrapolation of the results of the present study should be approached with caution. Finally, a word of caution about the use of Jak et al.'s *liberal criteria* for diagnosing MCI, despite entailing a potential increase in sensitivity, these diagnostic criteria raise some issues of false positive rate.

Understanding the association of performance in distinct MMSE cognitive domains to clinical diagnosis and to educational level is important to detect reliably the presence of cognitive impairment, considering the subject's education. The present findings do not support the view that some MMSE domains may generally be harder and more demanding for both cognitively impaired and less educated people. On the contrary, we found that impairment in specific MMSE domains pinpoints cognitive decline, probably indicating brain areas affected by neurodegeneration, and impairment in others reflects lower education levels and the lack of acquisition of relevant schooling abilities.

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