

BRAIN ATROPHY AND NEUROCOGNITIVE RESERVE- THE FIRST ROMANIAN CLINICAL STUDY

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INTRODUCTION

The brain reserve hypothesis (BRH) explains that high level of education and an active job/lifestyle could provide „cognitive reserve” which compensate the brain damage and the symptoms of neuropathological disorders occurring (Coffey et al., 1999; Satz, 1993). One direct empirical prediction of the BRH is that a higher cognitive reserve (corresponding with high educational level) will overcome or compensate for damage arising from disease or aging as demonstrated by higher than expected cognitive performance.

We studied the BRH using brain atrophy, level of education and cognitive level obtained from a sample of 235 individuals aged between 35 to 95 years old with cognitive complains who required neurocognitive evaluation at Bucharest Memory Center between 2011 to 2016.

The paper aims to verify whether higher education is associated with reduced cognitive decline (the cognitive reserve hypothesis).

We started from the hypothesis that for the same degree of cerebral atrophy and the same age, the average MMSE score increases with the level of education. For the same age and degree of atrophy, the level of studies has a significant effect on the MMSE score.

MATERIAL AND METHOD

Participants

A retrospective study was conducted over six years based on the medical records of those who addressed the Center for Memory for neurocognitive assessment in order to establish the diagnosis. For this purpose, the diagnostic criteria provided by the DSM IV R have been taken into ac-

BACKGROUND:

The cognitive reserve hypothesis explains the ability to tolerate the age-related changes and the disease related pathology in the brain without developing clear clinical symptoms or signs. Persons with a low educational level present earlier clinical symptoms of neuropathology disorders. The brain reserve moderates the relationship between changes at brain level and neuropathology disorders. Cognitive reserve could compensate the deterioration of the brain.

OBJECTIVE:

This study investigates the relationship between cognitive impairment level, the severity of brain atrophy and the level of education on a sample of 235 individuals with cognitive complains, who required neurocognitive evaluation at Bucharest Memory Center between 2011 to 2016.

METHODS:

A retrospective study was conducted over six years based on the medical records of those who addressed the Center for Memory for neurocognitive assessment in order to establish the diagnosis. The socio-demographic parameters were recorded along with educational level, the brain atrophy presence, the psychiatric diagnosis and cognitive decline.

RESULTS:

The cognitive reserve hypothesis was verified, unless the MMSE score was very low (for severe neurocognitive disorder). Thus, the cognitive reserve theory is confirmed by the relationship between the educational level and the Mini Mental Score Evaluation (MMSE) score (the higher the educational level is, the higher the MMSE score is).

Keywords: Brain atrophy, cognitive reserve, educational level, neurocognitive disorder

count. For mild neurocognitive disorders, the term Mild Cognitive Impairment (MCI) was also used.

235 patients who asked for neurocognitive assessment at the Center of Memory between January 2011 and November 2016 were included in the study. An ethanol dependent person was excluded from the study.

The following parameters were used: socio-demographic data, the level of education, the presence of the neuroimaging investigation and its results, the psychiatric diagnosis and the cognitive decline.

The neuroimaging cerebral investigation was computerized tomography (CT). From the outcome of the neuroimaging investigations, the presence or absence of atrophy was noted. The variables used in the research were: the atrophy type (cortical, subcortical and global), the degree of severity of cerebral atrophy: mild, moderate, severe, the symmetry of atrophy (symmetrical and asymmetric) and its localization (frontal, parietal, occipital, temporal).

41 people from 235 did not have neuroimaging investigations, and for 20 people the results of the investigation identified brain structures within normal limits.

A total of 174 persons were diagnosed with neurodegenerative pathology at various stages of disease level, 153 women and 82 men aged 35 to 95 years. Of the

153 female, 43 have low level of education, 68 have medium level of education and 42 have higher education. Of the 82 male patients in the study group, nine have low level of education, 34 have medium level of education and 39 have higher education.

For statistical analysis, IBM SPSS Statistics, Version 22.0 was used. In order to highlight the differences between the qualitative variables, the χ^2 test and Fisher's exact test were used. In order to quantify differences between groups in terms of quantitative variables we used the ANOVA parametric test, the Kruskal-Wallis non-parametric tests and the median test in the quantitative variables multiple comparison option. For a multidimensional approach of the variables we used the generalized linear model (GLM).

RESULTS

Distribution of the level of education differs significantly according to gender ($p = .002$, Fischer's exact test). Specifically: 46.9% of men presented at the Center of Memory have higher education, while only 27.5% of women have higher education (Figure 1a). Age distribution does not statistically significantly depend on the type of patients ($p = 0.82$ for the ANOVA test) (Figure 1b).

Figure 1a. Distribution of patients by gender

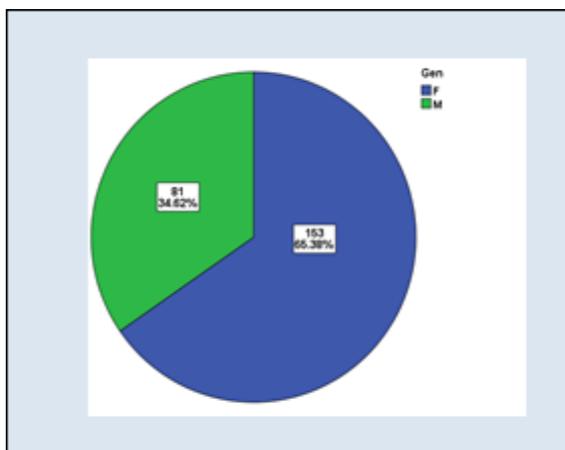
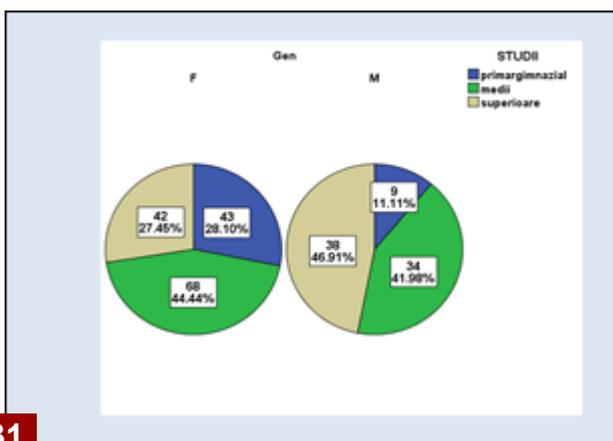


Figure 1b. Distribution of patients by gender and educational level



In order to evaluate the dependence of the MMSE score of all registered variables (including the neuroimaging variables), the generalized linear model (GLM) implemented in the SPSS software package was used. In this linear model were introduced the factors described in the literature that underlie the theory of cognitive reserve: level of education, degree of cerebral atrophy, level of cognitive impairment, as well as the localization and type of atrophy, the existence of vascular problems in the neuroimaging investigation, diagnosis, gender and age.

Of the 234 patients included in the study, the following were selected for this analysis: 1) patients who presented the result of the neuroimaging investigation; 2) patients with pathological changes detected by imaging; 3) patients with an MMSE score above 10 (the score of less than 11 is considered "severe" and occurs only in 6 patients in the database, insufficient for statistical analysis); 4) patients who do not have the degree of "severe" atrophy (considering that only one patient with severe atrophy meets the above mentioned 1-3 conditions). Under these conditions, only 166 patients were qualified for the following analysis. All selected patients show cerebral atrophy, so the data analysis can only be compared to "mild" and "moderate" atrophy rates.

Table 2 shows that variables with significant effect on the MMSE score are atrophy ($p < .001$ for the Fischer test), age ($p = .02$ for the Fischer test) and educational level ($p = 0.002$ for the Fischer test).

Table 3 restores variance analysis after eliminating variables with insignificant effect. The adequacy test shows that the model adequately describes the dependence of the variables ($p < 0.001$ for the Goodness of fit test). Table 3 shows the coefficients of the model after the deletion of the variables with insignificant effect. It is noted that all coefficients in the table are statistically significant ($p < 0.001$).

Interpretation of GLM results for the MMSE dependent variable in patients with mild or moderate atrophy and MMSE scores > 10:

1) The atrophy degree has a significant effect on the MMSE score ($p < 0.001$, Table 2). On average, the MMSE score is significantly higher ($p < 0.001$ for the t test) for mild atrophy versus moderate atrophy (by 4.54 higher in the analyzed case).

2) The MMSE score decreases significantly ($p = 0.017$ for the t test) with age. It should be noted that this result is important more theoretical and less practical: considering the 95% confidence interval mentioned in the table, 10 years of life decrease the average MMSE score with a small value: between 0.17 and 1.69.

3) The gender variable has an insignificant effect on the MMSE score.

4) If the degree of atrophy is known, the variables "presence of leukoaraiosis", "the presence of micro-lacunae", "the presence of territorial vascular accidents", →

Table 2. Univariate GLM analysis for the dependent variable MMSE and independent variable: gender, age, educational level, atrophy and diagnosis.

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	1612.62 ^a	14	115.19	6.25	.00	.37
Intercept	1941.30	1	1941.30	105.32	.00	.41
Gender	.84	1	.84	.05	.83	.00
age	105.46	1	105.46	5.72	.02	.04
education	246.61	2	123.30	6.69	.00	.08
Atrophy severity degree	756.68	1	756.68	41.05	.00	.21
symmetry of atrophy	.00	1	.002	.00	1.00	.00
the type of atrophy	11.59	2	5.796	.31	.73	.00
diagnosis	37.89	3	12.63	.69	.56	.01
Error	2783.43	151	18.43			
Total	99150	166				
Corrected Total	4396.05	165				

a. R Squared = .367 (Adjusted R Squared = .308)

Table 3. Univariate GLM analysis for dependent variable MMSE and independent variables: age, educational level, and atrophy degree

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	1508.45 ^a	4	377.11	21.03	.00	.34
Intercept	2080.88	1	2080.88	116.02	.00	.42
Age	104.96	1	104.96	5.85	.02	.04
Education	319.04	2	159.52	8.90	.00	.10
Atrophy	789.54	1	789.54	44.02	.00	.22
Error	2887.60	161	17.94			
Total	99150	166				
Corrected Total	4396.05	165				

a. R Squared = .343 (Adjusted R Squared = .327)

Table 4. Univariate GLM model for the dependent variable MMSE. Estimated parameters for significant independent variables: age, educational level, and atrophy degree

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
					Lower Bound	Upper Bound	
Intercept	30.32	2.94	10.30	.00	24.51	36.14	.40
Age	-.09	.04	-2.42	.02	-0.17	-0.02	.04
Education=low	-3.75	.91	-4.10	.00	-5.56	-1.94	.10
Education=medium	-1.99	.74	-2.69	.01	-3.46	-0.53	.04
Education=high	.00 ^a	.00	.00	.00	.00	.00	.00
Mild atrophy	4.54	.68	6.64	.00	3.19	5.89	.22
Moderate atrophy	.00 ^a	.00	.00	.00	.00	.00	.00

^a. Redundant values of the parameter

atrophy symmetry, atrophy type and diagnosis have an insignificant effect on the MMSE score.

5) For the same age and degree of atrophy, the level of education has a significant effect on the MMSE score (p < .001, Table 4): the MMSE score increases with the educational level. Concretely, the average MMSE score is significantly lower (p < .001, p = .008 for the t test) at the level of "low/medium", respectively "medium" compared to the "high" with 1,993 lower in the analyzed case).

6) The previous assertions 1) -5) confirm the hypothesis of

the cognitive reserve in the following detailed formulation: "For the same degree of cerebral atrophy and the same age, independent of a) gender b) symmetry / asymmetry of atrophy c) diagnosis, e) the presence of leukoaraiosis, f) the presence of microlacunae and g) the presence of territorial vascular accidents, the average value of the MMSE score increases with the level of education. "

This refers exclusively to patients with mild or moderate brain atrophy degree who, in addition, do not have a „severe" MMSE score. The volume of the sample analyzed was insufficient to obtain results relevant for patients with severe pathology.

For the multidimensional analysis of variables with significant influence on the MMSE score, the following samples were removed from the sample: 1) patients with incomplete data; 2) patients with an MMSE score of less than 10 (the score less than 10 is considered "severe" and occurs only 6 times in the database); 3) patients with "severe" atrophy (taking into account that one person cumulatively fulfills the conditions to be selected); 4) patients for whom the result of neuroimaging is "normal brain structures within the age". Under these conditions, 166 patients were qualified for the multidimensional analysis and all had cerebral atrophy.

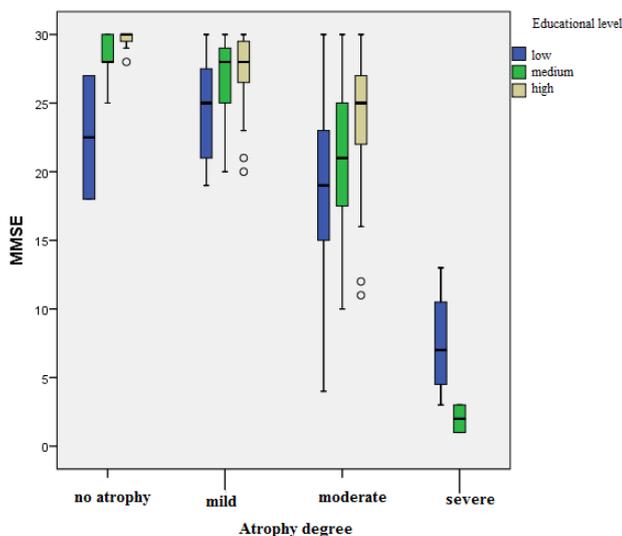
7) For severe atrophy, the MMSE score is low and shows severe neurocognitive impairment.

Table 5 and Figure 6 exemplifies and completes the assertions 1) -5). Thus, the type of atrophy does not significantly alter the mean MMSE score, as opposed to the absence of atrophy that significantly increases the mean MMSE score (p < .001 for the Kruskal-Wallis multiple comparison test).

Figure 6 graphically highlights the fact that, at the level of the analyzed sample, the MMSE score tends →

Table 5. Average MMSE score depending on the type of atrophy

Type of atrophy	Mean	N	Std. Deviation	Median
No atrophy	28.21	19	2.90	29
Subcortical atrophy	23.89	9	3.95	24
Cortical atrophy	23.21	116	6.62	25
Global atrophy	22.59	49	6.08	24
Total	23.58	193	6.27	25

Figure 6. Distribution of the MMSE score according to the degree of atrophy and the level of education

decrease as the atrophy increases and increases with the level of education. However, at individual level, the frequency of exceptions is high: 1) In many cases imagistic observation cerebral atrophy has no observable cognitive consequences at the MMSE score level; 2) the magnitude of MMSE values is high for patient population (for example, for moderate atrophy).

DISCUSSION

From the analysis of the relationship between the MMSE score and the degree of atrophy, the following conclusions were drawn:

- 1) The variables with significant effect on the MMSE score are: atrophy degree, educational level and age (Tables 2-4).
- 2) If the degree of atrophy is known, the other neuroimaging variables (for example, type atrophy, atrophy symmetry, the presence of leukoaraiosis, the microlacunel and regional cerebral vascular accidents) do not have a significant effect on the MMSE score.
- 3) In the presence of atrophy, the diagnosis has no significant effect on the MMSE score.

4) The patient's gender does not have a significant effect on the MMSE score.

5) On average, the MMSE score is significantly higher for mild atrophy compared to moderate atrophy.

6) On average, the MMSE score is significantly lower for the low and medium educational levels compared to higher education.

7) The MMSE score decreases significantly with age.

8) Multidimensional analysis confirms the hypothesis of the cognitive reserve, with the exception of patients who are included in the "severe" class according to the MMSE score classification, or according to the classification of the atrophy degree. More specifically: independent of the degree of cerebral atrophy, the effect of a higher level of education increases significantly the MMSE score.

It should be noted that high MMSE patients with early disease present imagistically cerebral atrophy - anatomical manifestation of the neurodegeneration process, which confirms the hypothesis of the cognitive reserve.

The data from the literature confirm the hypothesis of this study, so that the clinical symptoms of the disease occur earlier in people with a lower level of training and later in those with a high level of training and professionalism, the cognitive reserve acting as a moderator of the relationship between cerebral changes and the clinical profile of neurodegenerative pathology (Mortamais et al., 2014).

The influence of education in the development of neurodegenerative conditions was: stimulating cognitive lifetime may contribute to the increased density of synapses to stimulate neurogenesis to improve the efficiency and flexibility of neural networks to provide such protection of cognitive functioning under accumulation losses neuronal the extent of aging and the development of neurodegenerative pathology (Stern, 2009).

Recent studies (Stern et al., 2005) referred to compensatory, perhaps altered networks in older adults, as a manifestation of reserve. All considerable research until now shows that a number of factors including education, work complexity, social network, and leisure activities may contribute to this reserve allowing cognitive function to be maintained in old ages.

An important number of studies have also related these factors to the development of dementia, suggesting that intellectual challenges experienced across the whole life span may increase the brain reserve and be crucial for the occurrence of dementia symptoms in late life.

CONCLUSIONS

The cognitive reserve hypothesis was verified, unless the MMSE score was very low. Thus, the cognitive reserve theory is confirmed by the association between the educational level and the MMSE score (the higher the educational level, the higher the MMSE score).

Leisure activities, both physical, mental and social, seem to have the most beneficial effect and can cause delay in the onset of pathology and significantly reduce the number of cases of dementia in the community.

The higher education level, the complexity of work, and a mentally and socially integrated lifestyle in the last period of life could postpone the onset of a diagnosis of neurocognitive disorder.

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