ROMANIAN ACADEMY
Romanian Academy School of Advanced Studies
Institute of Philosophy and Psychology "Constantin Rădulescu-Motru"

SUMMARY OF DOCTORAL THESIS

NEUROPSYCHOLOGICAL PROFILES OF THE PROGRESSION OF MINOR COGNITIVE DEFICIT TO DEMENTIA IN ALZHEIMER'S DISEASE

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INTRODUCTION

Alzheimer's disease is often detected in mild to moderate dementia in a routine clinical setting at present. Emerging treatments addressing the pathophysiology associated with Alzheimer's disease are directed to the earlier stages of the disease and aim at maintaining cognition and functional independence in daily activities. The availability of such emerging treatments requires the identification of individuals with early-stage Alzheimer's disease in clinical, routine settings beyond academic centers and/or studies.

The priority areas for research should therefore include:

(1) elucidating the contributions of risk, demographic and sociocultural factors and the role that modifiable risk factors can play in the progression of cognitive problems;

(2) identification of areas, cognitive markers (e.g. memory, executive function, neuropsychiatric symptoms) that predict the risk of developing Alzheimer's disease and that distinguish the cognitive impairment due to Alzheimer's from other disorders;

(3) reaching a consensus on methodologies to define and assess the cognitive, behavioural and functional status of the target population;

(4) neuropsychological assessment batteries harmonized at European level;

(5) personalized intervention programs (e.g. increase in physical activity, treatment of concomitant depression) that may help reduce the severity of disability.

The purpose of the research was to investigate the role of cognitive markers in the continuum of Alzheimer's disease and to develop and implement an intervention strategy to improve cognitive deficits, maximize functional independence and a possible slowing of disease progression.

The thesis consists of two parts and is structured in 11 chapters. The first part addresses the aspects of the literature, focusing on the theoretical arguments that support the whole approach of research. The second part includes the chapters in which the studies and the solutions obtained in the research activity are presented.

In the first chapter - **The spectrum of cognitive changes from normal aging to Alzheimer's disease**, are presented the theories of aging, the risk factors underlying the emergence of cognitive decline and the stages of continuum from normal aging to dementia.

In chapter two - **Cognitive reserve**, passive and active models are presented that were the basis for building the concepts of cerebral and cognitive reserve and the importance of assessing cognitive reserve in clinical practice.

Chapter Three - **Neuropsychological Assessment** is dedicated to analysing the types of instruments used in cognitive evaluation and their importance in creating cognitive profiles that support differential diagnosis and monitoring the progression of the disease, from normal aging to dementia. Studies are ongoing at international and European level, aimed at achieving effective harmonization and optimization procedures in the use of cognitive, behavioural scales.

A systematic review of longitudinal cohort studies, reviews and meta-analysis studies, which evaluated the rates of progression of subjective cognitive decline to mild neurocognitive disorder and then to Alzheimer's disease, is performed in Chapter Four **Rates of Progression of Subjective Cognitive Decline to Mild Cognitive Disorder to Alzheimer's Disease**.

In Chapter Five - **The impact of the Covid-19 pandemic on people with dementia and the effects of SARS-CoV-2 infection on the population**, preliminary studies are presented from the literature, which analysed the effects of isolation and pandemic on people with dementia, but also the effects of SARS-CoV-2 infection on cognitive performance. Studies show symptoms of

"foggy mind", subjective memory complaints in people with normal cognitive status, and have reported high rates of people with dementia who have experienced an exacerbation or onset of neuropsychiatric symptoms.

Chapter Six is dedicated to the construction of the hypothetical model and the hypotheses of research studies.

In Chapter Seven, entitled **Assessment of cognitive reserve in normal aging elderly people**, the results of a study conducted for the purpose of verifying the hypothesis that **cognitive reserve and education levels are predictors of cognitive efficiency, with a detrimental effect on cognitive decline**.

In chapter eight - **Evaluation of the relationship between subjective cognitive decline and cognitive performance**, through the results obtained and the analysis of case studies, the hypothesis was verified that the **subjective perception of cognitive symptoms leads to over-reporting of cognitive problems.**

In Chapter Nine — **Building a battery of cognitive samples that can dynamically capture disease progression**, preliminary data from the battery application to a sample of normal cognitive individuals and a sub-sample of individuals with Alzheimer's disease are presented.

In Chapter 10 - **Development of an intervention strategy aimed at improving cognitive deficits, maximizing functional independence and a possible slowing down of disease progression,** are exposed different types of cognitive intervention. The stages of the development of the intervention strategy (programs with their modules) are presented, the effects of this strategy are assessed and its effectiveness in improving cognitive deficits is demonstrated.

In the final part of the paper - **Conclusions and final discussions**, the final results are summarized, which emphasize the importance of assessing the cognitive reserve, the factors influencing subjective memory complaints and the use of neuropsychological assessment batteries sensitive to the progression of cognitive decline. The importance of implementing intervention strategies aimed at slowing down the progression of the disease is also highlighted.

The main novelties brought by the research in this thesis are:

(1) From theoretical analysis and results of systematic review, rates of progression of subjective cognitive decline and mild cognitive impairment to Alzheimer's disease, neuropsychological profiles (cognitive markers) of the Alzheimer's disease continuum may be sketched.

(2) clinical, by creating the hypothetical pattern of follow-up of the progression of cognitive decline and highlighting the importance of introducing cognitive reserve in clinical evaluation. Cognitive function prediction is strongly dependent on the most accurate determination of preclinical cognitive status and cognitive reserve.

(3) practical, by implementing and validating a model of cognitive intervention and to counteract the worsening of cognitive symptoms.

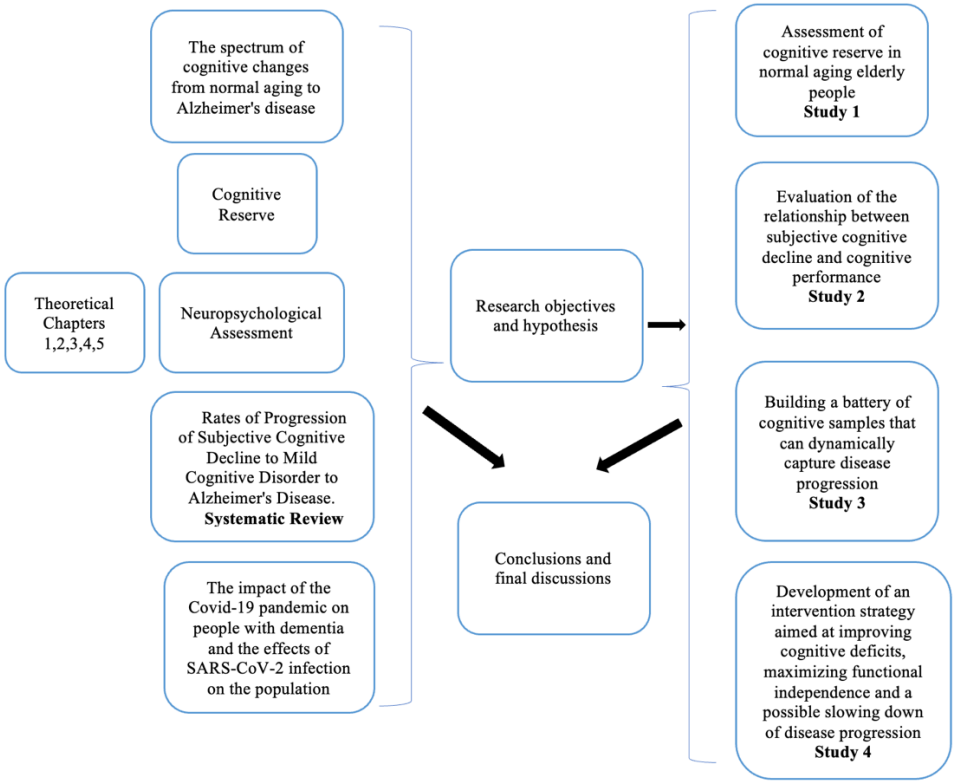

Figure 1. Structure of PhD thesis

Keywords: cognitive reserve, cognitive markers, dementia, Alzheimer's disease, mild cognitive impairment, subjective cognitive decline, cognitive stimulation

CHAPTER I. THEORETICAL FRAMEWORK

1. Theoretical model of Alzheimer's disease continuum

Based on currently available research (Reisberg et al., 1982; McKhann, et al., 2011), Alzheimer's disease is best conceptualized as a *continuum*, biological and clinical. Continuum (see figure 2) comprising the preclinical stage (individuals clinically asymptomatic but with disease specific biomarkers), mild cognitive disorder and clinical stage (symptomatic) distinguishing three Alzheimer's disease substages (Alzheimer's Association, 2020).

In the broadest possible sense, a *continuum* is defined as a smooth, uninterrupted sequence in which adjacent elements are not discernibly different from each other, even if the extremes are distinct.

In Alzheimer's disease, this continuum equates to the progression of the disease from an asymptomatic stage, through a long preclinical period in which pathophysiological changes are reflected by the increase of the biomarkers of the disease, to the symptomatic stage, during which changes in the biomarkers continue, and the cognitive and functional decline become increasingly evident, until partial loss of independence and eventually death.

These changes in the individual components of the continuum occur in a sequential but overlapping manner.

The following are the stages of the Alzheimer's continuum, as defined by the Alzheimer's Association (2020).

Figure 2. Continuum of Alzheimer's disease (adaptation to Alzheimer's disease facts and figures. 2020. *Note. BA - Alzheimer's disease*

A. Preclinical Alzheimer's disease

The preclinical stage of Alzheimer's disease continuum is characterized by the pathology of beta-amyloid, which can be detected by neuroimaging and analysis of cerebrospinal fluid (CSF) biomarkers in people without cognitive deficits (Jack, Bennett, Blennow, et al., 2018). In longitudinal studies, beta-amyloid accumulation in the brain in individuals without cognitive impairment was related to a higher risk of progression to mild cognitive disorder and dementia (Vos SJ, Xiong C, Visser PJ, et al., 2013; Insel et al., 2018).

It remains unclear, however, whether there is a specific threshold or a specific combination of biomarker abnormalities (beta-amyloid and tau protein) that can best predict the occurrence of clinical symptoms. Cognitive decline is likely to occur only when beta-amyloid accumulation is accompanied by other changes such as synaptic dysfunction and/or neuronal loss (van Rossum, et al., 2012; Ossenkoppele, et al., 2016).

B. Mild Cognitive Impairment (MCI)

In addition to the presence of biomarkers in the cerebrospinal fluid, patients with mild cognitive impairment have subtle deficits in memory and thinking. Mild cognitive impairment can improve, remain stable or progress to Alzheimer's disease or other types of dementia. In five-year observational studies in patients with mild cognitive impairment, 32% to 38% progressed to dementia (Ward et al., 2013; Mitchell and Shiri-Feshki, 2009).

The American Academy of Neurology recommends evaluating patients when they or a member of their family are concerned about a possible cognitive decline (Petersen, Lopez, Armstrong, et al., 2018).

Early diagnosis can improve healthcare delivery, and monitoring patients with mild cognitive disorder is important for staging the progression of cognitive decline (Foster, Bondi, Das, et al., 2019).

C. Major neurocognitive disorder secondary to Alzheimer's disease

The clinical sub-stages of Alzheimer's disease are mild, moderate and severe.

In **mild** sub-stage, most patients can function independently, but may require help. These patients are still able to drive and work.

In **moderate** sub-state, patients may have difficulties communicating and performing daily activities (clothing, daily hygiene). They may experience behavioural changes and mood disorders.

In the **severe** sub-state**,** patients need assistance with activities of daily living. The average survival time of people diagnosed with Alzheimer's disease, aged 65 years or over, is four to eight years, but it can reach up to 20 years (Alzheimer's Association, 2020).

Studies of the *continuum* concept of the disease are increasing, but its integration into clinical practice is not yet clearly defined and researched.

During this continuum some people will notice subtle changes in cognitive function before they become detectable in the currently available tests (Donohue et al., 2014; Jessen et al., 2014).

Cognitive trajectories vary significantly among individuals as they age, ranging from normal cognitive state to progressive impairment leading to dementia. The definition of normal cognitive function in older adults is surprisingly complicated due to variability in measurement patterns and individual differences (Park et al., 2002).

Figure 3 illustrates the decline of cognitive function with increasing age, pre-clinical stage, mild cognitive disorder (MCI) and dementia (Sperling et al., 2011).

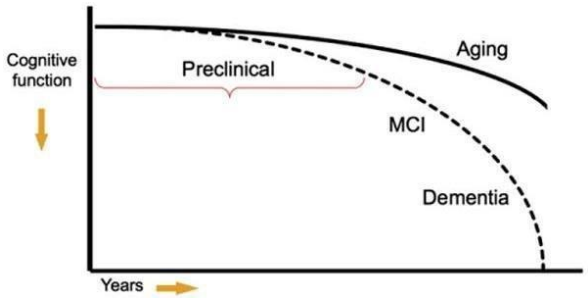

Figure 1 Cognitive function in the continuum of Alzheimer's disease *(Sperling et al., 2011).*

In recent years, emphasis has been placed on developing screening tools, cognitive assessment batteries, including tests/scales of cognition with as much fidelity as possible, capable of detecting subtle cognitive and functional deficiencies in preclinical stages. Instruments that can detect small changes in cognitive function to monitor the progression of the disease throughout the continuum.

It is important to understand which patients may be at greatest risk of progression to dementia, especially considering that preventive or palliative treatments, including both existing and emerging therapies, are likely to be more effective as they are applied sooner, before the emergence of multisystem cerebral atrophy (Crocco et al., 2018).

Several factors influence the emergence and progression of cognitive disorders, namely demographic, genetic, cardiovascular and psychosocial factors (Apóstolo et al., 2016). The factors related to lifestyle, healthy diet, exercise and cognitive training influence the cognitive reserve and the onset of cognitive decline. Cognitive reserve (CR) is the individual's ability to sustain cognitive function despite age-or disease-related brain changes (Stern, 2002, 2009; Rentz et al. 2010) and is malleable to old age (Lenehan et al., 2016).

A deeper understanding of these factors is crucial for the creation and activation of mechanisms to prevent and treat mild cognitive disorder and reduce the prevalence of its more advanced forms.

CHAPTER II OBJECTIVES AND GENERAL METHODOLOGY OF RESEARCH

Starting from the cognitive function model in Sperling's Alzheimer's disease continuum (Sperling et al., 2011) and the National Institute for Aging guidelines and Alzheimer's Association (Alzheimer Association, 2020) for staging the disease, we propose a hypothetical model of the factors that influence the evolution of cognitive function in the Alzheimer's disease continuum.

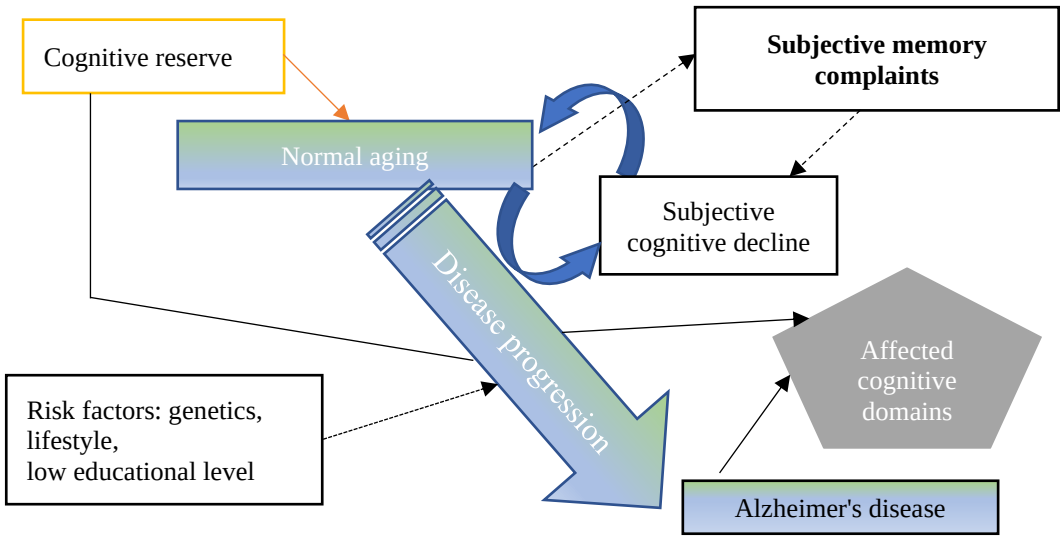

Figure 4. Hypothetical pattern of follow-up for cognitive decline progression

This model is applicable because it insists on:

- the cognitive reserve hypothesis that suggests that people can increase their resilience to disease pathology (Stern et al., 2012).
- that the cognitive reserve provides an explanation for individual differences in measured cognitive deficits despite similar degrees of neuropathology (Stern et al., 2012).
- the importance of subjective cognitive decline in research, individual clinical trials and in estimating groups of individuals at high risk of developing dementia.

The components of the model that formed the basis for the formulation of the objectives and assumptions of this research are:

A. Cognitive reserve. Living experiences, education, professional achievement levels and dynamic social networks can change cognitive function through cognitive reserve (Stern, 2002).

The importance of cognitive reserve in our hypothetical way lies in the following:

H1. individuals with greater cognitive reserve may have more resources available to face cognitive decline over time, resulting in a possible frantic role of CR in the trajectory of cognitive decline

H2. an increased cognitive reserve indicates a potential for masking early symptoms of cognitive disorder

Typical indicators of cognitive reserve include educational level, professional level, but also indirect measures such as lifestyle and social activities. Education is the most used parameter in studies of cognitive reserve (Nucci et al., 2011). Low level of studies is a well-established risk factor for dementia (Maccora et al. 2020).

B. Subjective Cognitive Decline (SCD)

The presence or absence of subjective cognitive decline cannot reliably determine whether someone throughout the aging process will continue or not to develop a neurocognitive disorder but can serve as a good starting point for the differential diagnosis between normal aging and mild cognitive disorder.

Potential alternative explanations for subjective perception of memory complaints in subjective cognitive decline in healthy individuals include sub-clinical symptoms of affective disorders, personality traits, lifestyle factors, or systemic illness.

Individuals with subjective cognitive decline may be more introspective and sensitive to perceived changes in their mental status.

Both cognitive impairment and subjective cognitive decline are closely related to the risk of progression to dementia. Cognitive reserve has mitigated the subjective cognitive decline associated with the risk of developing dementia (Jia et al., 2021).

C. Cognitive areas affected by cognitive decline

Dementia due to Alzheimer's disease is preceded by about five to six years of accelerated decline in multiple cognitive functions (Wilson et al., 2011).

The clinical presentation of dementia varies greatly from individual to individual, and the cognitive deficits it causes can present as memory loss, language disorders, agnosia (inability to recognize objects), praxis (inability to perform previously learned tasks), and impairment of executive function (reasoning, judgment, and planning). These deficits are the cognitive markers of the presence or progression of disease.

Some of these areas are given in Figure 6.

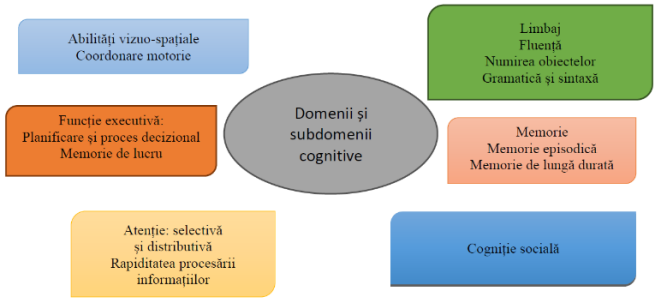

Figure 6. Cognitive domains affected by the progression of Alzheimer's disease

In accordance with our model, we consider that:

a. the evolution of cognitive function is nonlinear over time

b. The trajectory of each individual followed in the continuum of Alzheimer's disease is influenced by cognitive reserve

Due to its non-linear nature, the prediction of the evolution of cognitive function is strongly dependent on the most accurate determination of preclinical cognitive status and on cognitive reserve.

To achieve the goal, the research had the following **general objectives**:

1. Assessment of cognitive reserve in normal aging elderly people

2. Assessing the relationship between subjective cognitive decline and cognitive performance

3. Building a battery of cognitive samples that can dynamically capture the progression of the disease

4. Develop an intervention strategy aimed at improving cognitive deficits, maximizing functional independence and a possible slowing down of disease progression.

CHAPTER III. ORIGINAL RESEARCH

3.1 Study 1. Assessment of cognitive reserve in normal elderly persons

Introduction

The cognitive reserve concept considers individual differences in the sensitivity of age-related brain changes or brain pathology in Alzheimer's disease. There is evidence that some people can tolerate more of these changes than others and still maintain their cognitive function intact. Epidemiological studies suggest that life experience, including education, occupation, but also leisure activities, may increase this reserve.

Stern et al (2019) used the term "cognitive resilience" as a combination of brain reserve and cognitive reserve. Cognitive resilience helps combat aging and mitigates the impact of symptoms due to neurodegeneration (Stern et al., 2019).

Method

Instruments

In this study, the CRI-q **Cognitive Reserve Index** questionnaire was used to assess cognitive reserve used in most research studies, the Minimal Cognitive Status Assessment-2 (MMSE-2) and the Cognitive Assessment-Montreal Cognitive Assessment (MoCA) as cognitive efficiency tests.

A. The CRI-q questionnaire includes some demographic data (date and place of birth, sex, place of residence, nationality, marital status) and 20 items grouped in three sections: education, work and leisure, each of which creates a subscore.

The final version adapted to the Romanian language (R-IRCq) was administered to a subsample of 10 persons to check the understanding of the text. The results obtained suggested that individuals had a fluent understanding of each element.

Test-retest fidelity was analysed by the intra-class correlation coefficient (ICC), which was calculated by the correlation between the first and second completions of the R-IRCq questionnaire. Statistically significant was considered at $p < 0.05$. The alpha Cronbach coefficient of R-IRCq was 0.78 and the stability over time of the results, assessed by test-retest coefficients in a cohort of 40 subjects, was 0.87.

B. MMSE-2 (Minimum Cognitive Status Assessment-2) - MMSE-2® is a standardized clinical examination for cognitive impairment. The subjects of the exam are in the form of activities that mainly require the use of memory, as follows: Recording and Remembering, Orientation in time and space, Attention and calculation, Name, Repetition, Understanding, Reading, Writing, Drawing (https://testcentral.ro/test/mini-mental-state-examination-2nd-edition).

C. Cognitive Assessment - Montreal Assessment (MoCA) - was validated as a highly sensitive instrument for early detection of mild cognitive disorder (MCI) in 2000. MoCA has subsequently been adopted in clinical settings around the world and is widely used in academic and non-academic research. MoCA sensitivity for MCI detection is 90% compared to 18% for MMSE (Nasreddine et al., 2005). MoCA accurately and rapidly evaluates: short-term memory, visual spatial skills, executive functions, attention, concentration and working memory, language, temporo-spatial orientation. Test-retest fidelity (patients tested 35 days apart) was significant with an intracranial correlation coefficient of 0.92. Significant internal consistency was also found (alpha Cronbach 0.83).

D. Clinical Dementia Rating (CDR.)

It distinguishes five stages of disease severity: CDR. = 0: Healthy Subject, CDR. = 0,5: Uncertain Dementia, CDR. = 1: Mild Dementia, CDR. = 2: Moderate Dementia, CDR. = 3: Severe Dementia.

The information is obtained through a semi-structured interview with the patient and a caregiver. Six areas are evaluated: memory; orientation; judgment and problem solving; social behavior; socioprofessional behavior and personal care (https://monitorulpsihologiei.com/scala-de-evaluare-clinica-a-dementei-cdr-clinical-dementia-rating/).

Participants

Of the 146 participants, 105 were female (72%), 41 male (28%) aged 60-96 years (M = 74.61, SD = 7.12) and with primary to postgraduate studies (M = 3.08, SD = 1.54)

Procedure

All participants recruited for the study received the following battery of tests:

- Minimum Cognitive Status Assessment - MMSE-2;
- Montreal Cognitive Assessment - MoCA
- Cognitive Reserve Index Questionnaire in Romanian - R-IRC-q:
- Clinical Dementia Rating Scale - CDR. (applied by the psychiatrist)
- Semi-structured interview (performed by the neurologist): to examine and exclude the following pathologies with possible negative impact on cognition: known neurodegenerative diseases other than dementia, psychiatric, neurological and chronic syndromes, systemic disorders not compensated by pharmacological treatment, strokes, brain injuries and head trauma.

Each test took approximately 90 minutes, with breaks offered at the request of the participants. All participants signed a consent form declaring their voluntary participation in the research.

The Clinical Dementia Rating Scale (CDR.) was used to distinguish between healthy participants, with no evidence of cognitive impairment (CDR. = 0), and those with mild cognitive impairment (CDR. = 0.5) or Alzheimer's disease (CDR. = 1)

This measure was preferred to be used as a classification criterion because MMSE-2 and MoCA scores were used in the statistical model as result variables.

Data analysis

The study involves the use of a package based on descriptive, inferential and correlation statistics. The use of specialized statistical packages was called for in this regard: JASP 0.16.2 and IBM SPSS 21. To analyse the data and verify the hypothesis of this study we performed the following statistical procedures: correlation analysis, regression analysis and mediation analysis. The normality condition of the data was verified by graphical analysis of histograms and calculation of asymmetry and bolting indicators. Their compliance was verified against the values set out in the literature (Brown and Green, 2006; Blanca et al., 2013).

Results

The total scores obtained with the R-IRC-q questionnaire ranged from 67 (low cognitive reserve) to 161 (high cognitive reserve). Lowest scores were obtained on the leisure time subscore, even in those whose composite score indicated high cognitive reserve.

Mean and standard deviations of R-IRCq questionnaire scores (M=105.96, SD=21.03 and neuropsychological tests in our sample: MMSE-2 (M=27.85, SD=1.87), MoCA (M=24.36, SD=2.21)

All correlations between predictors and the two cognitive efficiency measures were significant by $p< 0.001$.

Significant inter-predictor correlations were demonstrated across the sample: both total R-IRCq score and study level are negative with age. Significant ($p < .001$) was the covariance between the age and the level of studies, which can be attributed to the specific socio-historical conditions of Romania (the increase in the general level of education during the lifetime of the participants in the study and the specific features of everyday life of the third age). This has also been observed by Nucci et al. (2011) at the time of the construction and validation of the questionnaire. The majority of older Italians did not have more than five years of study, due to social and/or historical reasons.

This study also confirmed a significant positive correlation between total R-IRCq score and level of education ($r = .75$, $p < .001$).

Also significant was the correlation between MMSE and MoCA scores ($r = .72$, $p < .001$).

As expected, age-related cognitive decline is more evident by MoCA score ($r = -.46$, $p < .001$) than by MMSE-2 score ($r = - .20$, $p = 0.013$).

We performed several linear regressions analysis to analyse the effects of predictors: age, study level, cognitive reserve on cognitive efficiency measures.

The first linear regression analysis investigated the correlation between age and dependent variables of the two cognitive efficiency measures (MMSE-2 and MoCA).

1. the regression equation was significant for MMSE-2 (adjusted $R^2 = 0.035$, $F (1.144) = 6.31$, $B = - 0.78$, $\beta = - 0.20$, $t = -2.512$, $p < 0.05$)

2. the regression equation was significant relative to MoCA (adjusted $R^2 = 0.21$, $F (1.144) = 39.83$, $B = - 1.49$, $\beta = - 0.46$, $t = - 6.311$, $p < .001$)

The predictive significance of the level of studies on the same measures of cognitive efficiency was evaluated in the second sandstone analysis.

1. the regression equation was significant for MMSE-2 (adjusted $R^2 = 0.094$, $F (1.144) = 15.98$, $B = 0.38$, $\beta = 0.31$, $t = 3.999$, $p < .001$)

2. the regression equation was significant relative to MoCA (adjusted $R^2 = 0.30$, $F (1.144) = 63.97$, $B = 0.79$, $\beta = 0.55$, $t = 7.999$, $p < .001$)

In the third sandstone analysis, the predictive character of the total R-IRCq score on the same variables was assessed.

1. relative to MMSE-2, the regression equation was significant (adjusted $R^2 = 0.073$, $F (1.144) = 12.37$, $B = 0.025$, $\beta = 0.28$, $t = 3.518$, $p < .001$)

2. the regression equation was significant relative to MoCA (adjusted $R^2 = 0.24$, $F (1.144) = 47.75$, $B = 0.053$, $\beta = 0.49$, $t = 6.911$, $p < .001$)

It is noted that the most significant predictor of MMSE-2 and MoCA scores is study level.

The fourth regression analysis evaluated the combined predictive character of predictors (age and total R-IRCq score) associated with the dependent variable (MoCA scores), regression equation was significant. The two predictors cover **32%** of the MoCA variance - model one, cognitive reserve (adjusted $R^2 = 0.24$, $F (2.143) = 47.75$, $B = 0.039$, $\beta = 0.36$, $t = 4.874$, $p < .001$) and model two, age (adjusted $R^2 = 0.31$, $F (2.143) = 34.94$, $B = - 0.0\ 97$, $\beta = - 0.31$, $t = - 4.107$, $p < .001$).

In the fifth regression analysis, the combined predictive character of predictors (age and study level) associated with the dependent variable (MoCA scores) was evaluated, the regression equation was significant. The two predictors cover **36%** of the MoCA variance (adjusted $R^2 =$

0.36, F(2.143) = 42.05, p < .001), age (B = - 0.08, β = - 0.27, t = - 3.77), and study level (B = 0.62, β = 0.43, t = 5.90).

We conducted two mediation analyses: having cognitive reserve as the mediator of age effect on cognitive MoCA performance and the level of studies as the mediator of age effect on cognitive performance (MoCA scores).

Results of the analysis (see tables 2 and 3) showed that there was a total effect of age on the MoCA score. This was statistically significant. Both study levels and total R-IRCq index partially mediate the effect of age on cognitive performance (MoCA). The model of the mediation analysis in both cases is shown in Figure 7 and 8.

Table 2. Mediation analysis: direct, indirect and total effects Age-IRC-MoCA

	β	z	p	95% CI for β
Direct effect				
Age - MoCA	0.044	4.15	<.001	-0.06, -0.02
Indirect Effect				
Age-R-IRCq-MoCA	0.022	3.70	<.001	-0.03, -0.01
Total effect				
Age - MoCA	0.065	6.33	<.001	0.08, 0.04

Note. MoCA - Montreal Cognitive Assessment; R-IRCq - Cognitive Reserve Index; CI - confidence interval. β - standardized regression coefficient, z - Sobel test (Sobel, 1982).

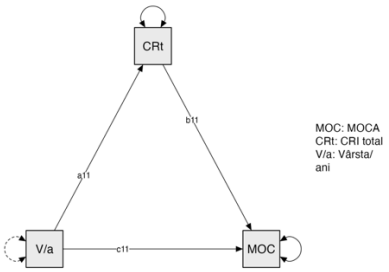

Figure 7. Median Age Analysis Model - R-IRCq (CRI) - MoCA

Table 3. Mediation Analysis: Direct, Indirect and Total Effects Age-MoCA Studies Level

	β	z	p	95% CI for β
Direct effect				
Age - MoCA	-0.039	3.81	<.001	-0.05, -0.01
Indirect Effect				
Age-level studies-MoCA	-0.026	4.15	<.001	-0.03, -0.01
Total effect				
Age - MoCA	-0.065	6:35	<.001	0.08, 0.04

Note. MoCA – Montreal Cognitive Assessment; CI - confidence interval, β - standardized regression coefficient, z - Sobel test (Sobel, 1982).

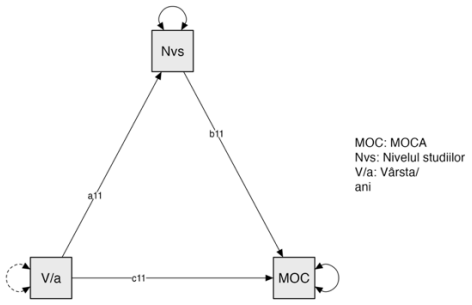

Figure 8. Mediation Age Analysis Model - Studies Level - MoCA

The mediating effect of the level of studies is due to the correlation with the age, determined historically, mentioned above.

A case study was analysed to explain the hypothesis that an increased cognitive reserve indicates a potential to mask early symptoms of cognitive impairment. Woman, 87 years old, higher education, high cognitive reserve (R-IRCq -130), simple cognitive assessment results MMSE-2 = 25/30, previous depressive episode. On the extended neuropsychological evaluation MoCA - 23/30; Trail-A – 43 sec, with 3 faults; Trail-B – 170 sec, with 5 faults; Figure Benson copy – 10, memory – 8; Phonemic verbal fluency letter L – 4 words. The scores, although lower compared to those from the initial assessment, are still considered at the age limit, compatible with depressive mood, but she was given the diagnosis of mild cognitive impairment under observation.

The brain MRI result suggested a significant reduction in cortical volume and, nucleocapsular, subinsular and thalamic regions. This result is consistent with a person diagnosed with moderate to advanced dementia.

Discussions and conclusions

The primary outcome of this study was that cognitive efficacy was predicted by age, study level, and total R-IRCq score. The inverse correlation between age and cognitive efficiency has been confirmed: the older the age of participants, the lower the cognitive efficiency, the more significant the correlation when cognitive efficiency is measured using MoCAs.

A significant correlation between study levels and cognitive efficiency measures has been confirmed. Both study levels and total cognitive reserve index (R-IRCq) are significant predictors of cognitive efficiency measures. Age and total cognitive reserve index (R-IRCq) cover 32% of MoCA variance. Age and study level cover 36% of the MoCA variance. Both study levels and total R-IRCq index partially mediate the effect of age on cognitive performance (MoCA).

The assessment of cognitive reserve in older people could be a useful additional measure to integrate into existing neuropsychological assessment protocols of cognitive decline (Buzdugan, 2022, in course of publication).

The results of this study are consistent with other data from the literature and the study of analysis of cognitive reserve and cerebral atrophy in patients with neurodegenerative disorders, Moglan, Boscarium and Tudose (2021). They noted that cognitive reserve acted as a moderator of the relationship between brain changes and the clinical profile of neurodegenerative pathology (Rada and Marinescu, 2021).

3.2. Study 2. Assessment of the relationship between subjective cognitive decline and cognitive performance

Most people notice some cognitive changes, which occur with increasing age. Between 50% and 80% of people aged between 50 and 70 with scores in the normal range on cognitive tests, report a perceived form of decline in cognitive functioning when asked (Jessen et al., 2010).

The concept of subjective cognitive decline could change the diagnosis and ineffective treatment of late-stage Alzheimer's disease into a more effective prophylactic strategy. Emotional state could affect the diagnosis of subjective cognitive decline.

In this context, we assume that (H0) **subjective perception of cognitive symptoms leads to over-reporting of cognitive problems.**

To verify this hypothesis, we have carried out the following steps:

1. Assessing the contribution of different factors related to subjective memory complaints to individuals with subjective cognitive decline.

2. Correlation between the level of subjective memory complaints and performance on cognitive tests.

Methods

Instruments

A. *Subjective memory complaints questionnaire (SMCQ)*

The SMCQ questionnaire is made up of 14 items that reflect different aspects of subjective memory complaints, including metacognition of general and specific memories. Four items were designed to evaluate memory globally and ten to evaluate memory function in day-to-day tasks. To increase the fidelity of each item, responses were limited to YES or No.

Example of item from CPSM questionnaire validated and adapted in Romanian.

"Do you think you have problems with your memory?"

"Do you think your memory is lower than that of other people of the same age?"

"Having trouble remembering a conversation you had a few days ago?"

B. *Questionnaire for the evaluation of prospective and retrospective memory - PRMQ*

The PRMQ questionnaire is made up of 16 items (Smith et al. 2000), which was developed to provide a scale of self-reporting of prospective and retrospective memory from everyday life. Eight items are on prospective memory and the other eight on retrospective memory.

Example of item in PRMQ questionnaire (short term, prospective memory):

"Do you happen to want to do something in the next few minutes and then forget it?" (https://www.ed.ac.uk/files/atoms/files/prmq-romanian.pdf)

Example of item in PRMQ questionnaire (long-term, retrospective memory):

"Do you happen to no longer recognize a place you've been to?" (https://www.ed.ac.uk/files/atoms/files/prmq-romanian.pdf)

C. BDI-II - Beck Depression Inventory - Second Edition (BDI - II) *(Beck Depression Inventory - Second Edition)*.

D. DASS-21R - Depression, anxiety and stress scales.

F. Route Test A and B - Route Test is a neuropsychological test of visual attention. It can provide information about visual search speed, processing speed, mental flexibility, as well as executive function.

G. Categorical verbal fluency test - Animals - the patient must generate as many words as possible from the semantic group - animals in one minute.

Participants

Inclusion criteria for this study are subjective complaints of memory and normal cognitive level and age ≥45 years.

Exclusion criteria are mild cognitive disorder, dementia, major psychiatric disorders (i.e., current depression, personality disorders, schizophrenia), known neurological diseases causing memory impairment (i.e., Parkinson's disease, epilepsy), HIV, alcohol abuse or other substances.

120 participants were between 45 and 78 years old, and 56 were female. Participants had an average of 12 ± 4 years of education, and 72 had a family history of dementia.

Procedure

All participants received a neuropsychological evaluation with MMSE-2, questionnaires for subjective cognitive decline, Beck Depression Inventory (BDI-II) and DASS-21 R as part of the core investigation, and an additional neuropsychological evaluation (average time between assessments 40 days) covering the following cognitive areas: language, attention, executive functions, and visuospatial skills.

Data analysis

The study involves the use of a package based on descriptive, inferential and correlation statistics. The use of specialized statistical packages was called for in this regard: JASP 0.16.2 and IBM SPSS 21. To analyse the data and verify the research hypothesis we performed the following statistical procedures: correlation analysis and regression analyses. We evaluated the basic characteristics of the studied population and evaluated the differences between the categories of participants, using chi-square tests or ANOVA, adjusted for age and gender, as appropriate.

We performed a test-test analysis for CPSM and PRMQ questionnaires. The test-correlation value for CPSM is 0.98 and for PRMQ is 0.99, both significant ($p < .001$).

Results

Most participants reported cognitive decline, which appears substantially higher than in the general population.

In the interviews and in the initial results I found that a higher cognitive complaints report was associated with a poorer quality of life, suggesting that subjective complaints have a negative effect on the overall sense of well-being. On the other hand, we cannot rule out reverse causation, as poorer quality of life may also affect subjective appreciation of cognitive abilities.

A positive correlation was obtained between the two questionnaires of subjective memory complaints ($r=.63$, $p < .001$). TMTA with PRMQ ($r=.23$, $p < .005$) and CPSM ($r=.41$, $p < .005$); TMTB with PRMQ ($r=.30$, $p < .001$) and CPSM ($r=.58$, $p < .001$) were also positive associations between the tests of attention and executive function.

We performed univariate linear regression analysis to evaluate associations between subjective cognitive complaints and neuropsychological test scores (table 4).

Table 4. Regression analyses (PRMQ, CPSM and neuropsychological tests)

Variables	R^2	F	df	B	β	t
PRMQ						
MMSE-2***	0.12.	16.57	1.118	0.07	0.35	4.07
TMTA*	0.05	6,67	1.118	0.15.	0.23.	2,58
TMTB***	0.09	12,24	1.118	0.86	0,30	3,49
Fluency, semantics - animals ***	0.09	11,85	1.118	0.10	0.30	3.44
CPSM						
MMSE-2***	0.29	50,21	1.118	0.20	0.54	7.08
TMTA*	0.17.	24,67	1.118	0.49	0.41	4,96
TMTB***	0,34	62,38	1.118	2,94	0.58	7,89

Fluency, semantics - animals ***	0.27	43,98	1.118	0.32	0.52	6.63

Note. *** p < .001, * p < 0.05

Cognitive test scores predict to a significant degree subjective memory complaints, but especially in the case of CPSM questionnaire score.

In our sample, 44% had anxiety symptoms and 38% had depressive symptoms. The percentages of symptoms associated with subjective memory complaints are shown in Tables 5 and 6.

Table 5. Percentage of anxiety symptoms in the sample and subjective memory complaint scales

Percentage with moderate anxiety in the sample	Percentage with moderate anxiety in the sub-sample, PRMQ threshold score	Percent with moderate anxiety in sub-sample, CPSM threshold score
44%	54%	45%

The percentage of people with moderate anxiety and threshold scores at PRMQ is significantly higher than the percentage in the sample. The percentage of subjects with moderate anxiety and CPSM threshold scores is not significantly higher than the percentage in the sample.

Table 6. Percentage of depressive symptoms sampled and subjective memory complaint scales

Percentage with mild depression in the sample	Percent with mild depression in sub-sample, PRMQ threshold score	Percent with mild depression in sub-sample, CPSM threshold score
38%	39%	36%
Percentage with moderate depression in the sample	Percent with moderate depression in sub-sample, PRMQ threshold score	Percentage with moderate depression in the sub-sample, CPSM threshold score
13%	13.5%	7%

The proportion of subjects with mild and moderate depression and threshold scores at PRMQ did not differ significantly from the proportion of subjects in the sample. The proportion of subjects with mild and moderate depression and CPSM threshold scores is significantly lower than the proportion of subjects in the sample.

A higher score on subjective memory complaint questionnaires was related to the presence of affective symptoms (anxiety and depression).

In our sample 59% of participants had a history of Alzheimer's disease in the family, 3% had higher scores (longer pregnancy time, more than 180 seconds) in the Trail Making Test B and 15% had scores below the threshold (less than 15 words/minute) in the categorical verbal fluency (animals) test.

The five case studies analysed support the importance of evaluating subjective memory complaints and the need to integrate subjective cognitive decline and neuropsychological assessments into clinical practice for monitoring people at risk of developing Alzheimer's disease.

Discussions and conclusions

Subjective cognitive complaints were found to be related to the presence of affective symptoms; this finding confirms the results of earlier studies (Slot et al., 2018). It has been confirmed that individuals with high levels of anxiety are more likely to experience subjective cognitive decline.

59% of participants with subjective cognitive complaints had a history of Alzheimer's disease in the family. Thus, we can conclude that anxiety related to the family history of dementia, rather than the real experience of cognitive decline by interpreting memory problems as clinical signs of dementia, may be a reason to present themselves to a specialist control (Buzdugan, 2021).

The conception of concern about the risk of developing Alzheimer's disease (Warwick and Salkovskis, 1990) is consistent with existing health anxiety models, which assume that personal experience with a disease can lead to selective attention to symptoms and therefore to increased health-related anxiety (Buzdugan, 2021).

The limits of this study are related to the small group of participants, the failure to introduce personality and quality of life questionnaires in the study, but also the lack of neuroimaging and beta-amyloid status, to corroborate the results and obtain a differential diagnosis as faithful as possible.

3.3. Study 3. Construction of the "RECOG" Neuropsychological Evaluation Battery

The definition of normal cognitive function in older adults is surprisingly complicated due to variability in measurement patterns and individual differences. For example, in a cross-sectional study of 345 people aged between 20 and 92, Park et al. (2002), showed that while performance at testing multiple cognitive domains - including reasoning, working memory, and processing speed - declines throughout life, it increases performance at semantic memory tests. Accurate measurement of cognitive function requires careful sampling and assessment of factors that may affect cognition.

In short, measuring cognition for the purpose of a clinical trial is a complex issue and should be adapted to the studied population and to the specific objectives of the project.

Neuropsychological research on dementia has focused on the evaluation of mild cognitive disorder and dementia in Alzheimer's disease, since it is the most common cause of dementia.

Longitudinal assessment scores can help to stage cognitive trajectories, when a person is experiencing cognitive decline, temporary deficits or maintains a stable cognitive level.

Methods

Instruments

Through the **ReCOG** neuropsychological evaluation battery we aim to evaluate more cognitive areas.

A. Global cognitive level. We used as a global cognitive rating scale in the first stage MMSE-2 (standard version), then the MoCA cognitive screening test. The MoCA test is much more difficult than the MMSE-2 (standard version) and therefore it is more likely to detect subtle cognitive deficits. In addition, the effects of low and high scores are less common in MoCA, which also allows a broader range of scores for people with mild cognitive impairment than MMSE-2. On the other hand, MoCA can be used to distinguish between people experiencing a typical age-related cognitive decline and those experiencing mild amnestic cognitive disorder (Hemrungrojn et al., 2021). The total score on the MoCA is 30 points.

B. Tests for the assessment of episodic memory

Research has highlighted the importance of measuring episodic memory, such as learning word lists and storytelling, in assessing dementia. Thus, in the ReCOG battery we decided to introduce: memorizing a story from the extended version of MMSE-2 (it is normalized and validated on the population of Romania); a non-verbal memory sample (reproduction from memory of the Benson figure) - this sample also has a component in the visual-spatial abilities sample. In the drawing test from memory figure Benson - the patient must reproduce, after a period of time, the drawing from memory, in order to achieve an alternative version (10-word memorization list), we translated and received the agreement to use the CERAD battery (Consortium for the establishment of a registry of Alzheimer's disease)

C. Tests for language evaluation (semantic memory)

Verbal fluency tests: categorical and phonemic (animals, vegetables, letters L and F).

The categorical verbal fluency implies that the patient must generate as many words as possible from the semantic group of animals (A) and vegetables (L) in one minute. Phonemic verbal fluency implies that the patient generates in a minute as many words as possible starting with the letter L and F (these words must be common nouns). The best-known phonemic verbal fluency sample is that of the letters F, A and S (FAS) (Strauss, Sherman and Spreen, 2006).

D. Tests for the assessment of visualization-spatial abilities

Visual-spatial deficits subsequently arise from episodic memory deficits in Alzheimer's disease, but they may occur prior to episodic memory deficits in the dementia of posterior cortical atrophy and those of Lewis bodies. This creates distinctive profiles of the cognitive performance of people with Alzheimer's disease and other types of dementia. Introducing the copy sample of the Benson figure helps to such discrimination.

The Benson Figure Copy Reproduction Test - simplified form of the "Rey-Osterrieth Complex Figure" test, aims to evaluate visuo-spatial and constructive abilities.

E. Tests for immediate attention, working memory and executive functions

Memory of numbers - The memory burden of numbers is derived from evidence included in intelligence measurement tests such as the Wechsler Intelligence Scale for Children (WISC) and the Wechsler Adult Intelligence Scale (WAIS).

Direct digital span forward (DSF) playback - series of numbers that the patient must repeat in the same order in which it was told by the assessor.

Digit span backward (DSB) - series of numbers that the patient must repeat in reverse order of how it was told by the evaluator.

Trail making test A and B. The Trail making test is a neuropsychological test of visual attention. It can provide information about visual search speed, processing speed, mental flexibility, as well as executive function. It was originally part of the Army's individual test battery (Armitage, 1946).

The fidelity and validity of the original versions of the battery included tests are significant and have been described in detail in neuropsychological test compendiums such as those published by Lezak, Howieson and Loring (2004) and Strauss, Sherman and Spreen (2006). The usefulness of the original versions of the tests for the early detection of Alzheimer's disease (or MCI), aiming at the progression of the disease and exploring the relationship between the specific cognitive deficits of the pathology of Alzheimer's disease was described in various studies (Salmon and Bondi, 2009).

Participants

Out of the remaining 233 participants we formed two groups (group with normal cognitive level) NC = 201 people (146 women and 55 men) and Alzheimer's disease (AD) = 32 people. The average age of participants was 76.30 (SD = 10.17).

Procedure

All participants (NC and BA) and caregivers participated in the initial visit. During this visit, participants received MMSE-2 for eligibility purposes followed by a clinical evaluation. Participants completed a depression questionnaire (Beck Depression Inventory - BDI-II). The medical history was reviewed in a full clinical interview. Clinical diagnoses were allocated by a psychiatrist/neurologist based on all data collected at baseline and CDR. scores.

At 30 days, participants in the (normal cognitive) NC and AD (Alzheimer's disease) groups received the ReCOG battery.

Data analysis

The study involves the use of a package based on descriptive, inferential and correlation statistics. The use of specialized statistical packages was called for in this regard: JASP 0.16.2 and IBM SPSS 21 and MEDCALC. To analyse the data and verify the research hypothesis we performed the following statistical procedures: correlation analysis, regression analysis and logistic regression.

First, we assessed the validity of the translations in Romanian and linguistically adapted to the cognitive tests, in the following ways:

(1) criterion validity was assessed using the analysis of covariance to compare the differences in scores in cognitive tests between the participants of AD and NC on age, educational level and gender. By comparing the scores averages of the groups NC and AD, we can conclude that the level of the studies influences the scores obtained in the battery cognitive tests;

(2) construct validity has been examined using Pearson correlations between selected cognitive tests;

(3) diagnostic validity by assessing the discriminatory point and the characteristics of the recipient operator (sensitivity and specificity) of cognitive tests when differentiating between healthy cognitive control (NC) groups and persons with Alzheimer's disease;

(4) test-retest fidelity could not be assessed due to pandemic quarantine measures, disease and death, but also to new variables that arose during the quarantine period, such as anxiety, depression and social isolation.

Results

The gross scores obtained by each participant can be converted to standard z scores using gender, age and level of education, according to the model below.

Table 7. Model for calculating Z-scores by age, gender and education

	NC	AD
	M	M
Zscore: Genre	- 03069	,19278
Zscore: Level of studies	,03723	- 23386
Zscore(rec_age)	- 01350	,08277

Many of the sub-tests used are similar to items found in other validated assessment tools. The number seven series in the MoCA is similar to that in the MMSE-2, but also to the items that assess attention and focus in the Wechsler Memory Scale, Revised (WMS-R, 1987). The MoCA cube drawing item is like the MMSE-2 and the Benson figure copying test (which is a simplified version of the "Rey Complex Figure" test, 1941), like the Benton Visual Memory Test items (BVRT, 1974). Categorical verbal fluency subtest animals and vegetables with items from WMS-III (1997) and phonemic verbal fluency subtest F and L with items from the FAS test (Strauss, Sherman and Spreen, 2006).

Memory of Figures sub-tests - the original samples included in intelligence measurement tests such as WISC (Wechsler Intelligence Scale for Children) and WAIS (Wechsler Adult Intelligence Scale for Adults), have recently been validated as items in the Memory of Objects and Figures Test and examination of the falsification of Menzic Performance - MODEMM (Sava and Crișan, 2022).

The Memory of a Story item is part of the MMSE-2 extended version test (red form). It has already been validated on the population in Romania (Minimal Cognitive Status Assessment 2, Folstein et al., Munteanu, Iliescu, Livinți, 2013).

(2) the construct validity has been examined using the Pearson correlations. The normality condition of the data was checked at Forbet by inspecting the graphical inspection of histograms, and by calculating the asymmetry (skewness and kurtosis) indicators.

Positive correlations between the subtests and the MoCA scale were established in this study, the only negative correlations are between the TMTA and the TMTB (Route Test A and B) subtests, as expected. Higher scores in these subtests indicate weaker performance.

The correlations between the battery sub-tests ReCOG and MMSE-2 are as follows: with MoCA (r = .87), with TMTA (r = - .79), with TMTB (r = -.84), with Story Remembrance (r = .57), with DSF (r = .74) and DSB (r = .72), with figure Benson Copy (r = .72) and reproduction from memory of fig. Benson (r = .84), with verbal fluency animal category (r = .83) and vegetables (r = .76), with phonemic verbal fluency F (r = .79), L (r = .81) and phonemic verbal fluency F&L (r = .80). All correlations were significant at 0.01.

To estimate the effects of predictors, gender, age, and education on cognitive test scores, we performed several regression analysis models (see Table 8).

In the regression analysis models the following conditions were verified and met: by graphical analysis - normality of dependent variables and the diagnosis of collinearity by analysis of variation inflation factor (VIF) values in the table "Coefficients". All values obtained are less than 10, thus avoiding multicollinearity.

Table 8. Effects of gender, age and education predictors on cognitive test scores

Cognitive scales	gender	age	education
MoCA	.03	**- .23**	**.35**
Storytelling	-04	**- .18**	**.56**
TMTA	- .09	**.44**	**- 36**
TMTB	- .01	**- .37**	**38**
DSF	.12	- .09	**.40**
DSB	.08	- .05	**.40**
figure Benson Copy	-05	.09	.13
figure Benson reproduction drawing in memory	.02	**- 23.2**	**.19**
animal categorical verbal fluency	- .04	**- .20**	**.34**
categorical verbal fluency vegetable	**- .27**	.13	**.21**
phonemic fluency L	- 17	-06	**29**
phonemic fluency F	- 15	-06	**.29**
L&F total phonemic verbal fluency	- 17	-06	**.30**

Note. Significant effects at $p < .001$ and 95% CI are denoted in bold in the table

Age and education are statistically associated with many of the cognitive test scores. For almost all tests except Trail making Test A and B, an increase in age is associated with lower test scores, i.e., lower performance. This was to be expected for these tests because a higher score (i.e., slower execution) means a lower performance.

(3) Logistic regression analyses were performed to identify the subset of cognitive tests that best described differences between NC and AD cases. Classification statistics (sensitivity, specificity) and the characteristic receptor curve (AUC-ROC) were generated for each model set. The diagrams of the ROC analyses are shown in Figure 9. All cognitive test scores were compared to MMSE-2 scores, which were used as the standard test.

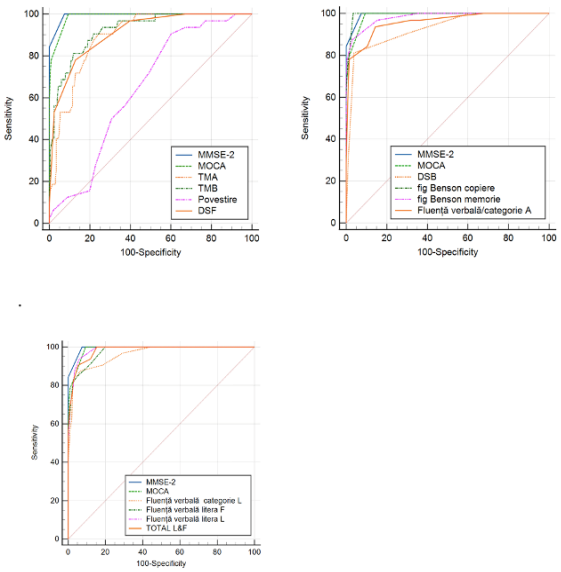

Figure 9. Graphs of ROC analyzes (and comparisons between cognitive samples)

Most of the cognitive tests used in the neuropsychological battery had good sensitivity and specificity. The overall MoCA score correctly classified NC and AD cases with 100% sensitivity and 90% specificity. Memory test scores had a sensitivity of 92% and specificity of 99%; executive function test score, sensitivity 81% and specificity 96%; attention test score, sensitivity 90% and specificity 75%; language test score, sensitivity 93% and specificity 80%; visual-spatial skills test score, 100% sensitivity and specificity 96%.

Diagnostic sensitivity of cognitive tests in the classification of patients with dementia compared to healthy subjects is compared in Table 9.

Table 9. Diagnostic sensitivity of cognitive tests dementia patients versus healthy controls

	MoCA	**Pov**	**TMTA**	**TMTB**	**DSF**	**DSB**	**FBC**	**FBM**	**FVCA**	**FVCL**	**FVL**	**FVAC**	**FVTLV**
ANOVA													
F	35.49	4.5	142,35	199,27	89,40	94,36	451.83	377.13	220.24	191.96	275.51	276.59	281.56
p	<.001	0,034	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Estimate **size of effect**													
UH²	0.52	0,013	0.25.	0,34	0.23.	0.24.	0.65	0.58	0.43	0.44	0.51	0.52	0.52
AUC	0,98	0,64	0.89	0.92	0.90	0.92	0.96	0,98	0.92	0.95	0.96	0.97	0,98

Note.
Pov - Storytelling; TMTA – Tral Making Test A; TMTB – Trail Making Test B DSF - digit span forward DSB - digit span backward FBC - figure Benson copying FBM - figure Benson memory FVCA - word fluency animal category FVCL - word fluency vegetable category FVLL - phonemic word fluency L FVLF - phonemic word fluency F FVTLF - total phonemic word fluency L and F AUC - area under the curve ROC

Discussions and conclusions

This study describes an initial set of data collected from a sample of subjects with normal cognitive status and a subset of individuals with Alzheimer's disease.

Further data and analysis on a much larger sample with greater stratification of participants by age group will be needed to develop normative sets for this neuropsychological battery. Cognitive tests in the neuropsychological battery differ from how they are influenced by age. This is consistent with the findings of other studies that studied the effect of aging on cognitive levels. The results also suggest that education has a very strong effect on cognitive performance and confirm earlier research (Manly et al., 1999; Byrd, Sanchez and Manly, 2005).

Most of the cognitive tests used in the neuropsychological battery had good sensitivity and specificity. Neuropsychological evaluation remains an essential step in the diagnosis and characterization of patients with mild cognitive disorder and Alzheimer's disease. Much more sophisticated tools using available IT technologies, such as touch screens and interactive programs, provide an exciting opportunity to further improve our assessment methods. Computer neuropsychological testing can be used to create short and sensitive tests, especially for use with subjects with normal cognitive level and those with mild cognitive impairment. However, the development of such measures is costly and requires more specialists and resources, but this may be an interesting direction in the further expansion of this research.

3.4. Study 4. Develop an intervention strategy aimed at improving cognitive deficits

A major approach to reducing the prevalence of Alzheimer's disease is to develop strategies to delay its occurrence in people at risk of developing dementia. Mild cognitive disorder is a transition phase between normal aging and dementia. This prodromal stage of dementia is recognized as a key period for the possibility of interventions to stimulate cognitive reserve and counter the worsening of cognitive symptoms (Albert et al., 2011). The limited efficacy of current drug therapies in MCI stimulated an increasing interest in the use of cognitive intervention in mild cognitive disorder.

Cognitive intervention

Clare and Woods (2004) describe three different types of cognitive intervention: cognitive training, cognitive rehabilitation, and cognitive stimulation. Cognitive training refers to standard guided tasks to develop cognitive function. Cognitive rehabilitation focuses on improving some cognitive areas. Finally, cognitive stimulation includes participation in cognitive activities, individually or in groups, aimed at improving and maintaining social and cognitive activity.

Cognitive stimulation includes activities such as spatial and temporal orientation, memory exercises, leisure activities. These three types of interventions are based on one-way interventions (single-domain focus). Multimodal cognitive interventions are generally complex interventions, encompassing physical, social and psychological components.

The findings of Alves et al., 2014, suggest that cognitive stimulation can have significant effects, even in the absence of cognitive or functional improvement.

These types of complementary interventions are frequently used interchangeably despite having different meanings, objectives and consequences. The choice for using one of them depends on the purpose of the intervention and the cognitive profile of the patient (Buschert et al., 2011).

Methods

The current study proposes an alternative approach to existing cognitive training programs. The intention here was to provide individuals with mild cognitive impairment with a cognitive stimulatory environment, using a range of new activities.

There are two lines of evidence to support the usefulness of cognitive stimulation in this regard.

The first is based on the concept of cognitive reserve. The Cognitive Reserve hypothesis proposes that lifelong experiences, including education, the complexity of occupation, and involvement in cognitive stimulation activities, result in a greater reserve.

The second is based on the usefulness of social and family support, with the program adopting a dyadic approach that involved the inclusion of a support person. This dyadic approach has the advantage of promoting social interaction, as well as of individualizing the treatment, adapting it to the neuropsychological abilities of a participant.

Although this program was originally designed to be run in physical format, due to the pandemic and quarantine period, it was run online.

The specific steps for achieving the overall objective of this study supported the entire research approach.

1. Creation of the program and cognitive stimulation specification (modules one-six)
2. Creation of the kinesiotherapy program together with the specialist who implemented this program (module eight)
3. Creating the creative module through acting, together with the specialist (new module)
4. Choosing interactive games and incorporating them into the stimulus program, so that each of them is involved in the activation of a cognitive domain (module seven).

Participants were eligible if, following clinical evaluation by the neurologist, they had received the diagnosis of mild cognitive disorder, no visual and hearing disorders. 17 participants were included in the study, 14 women and 3 men. The average age of participants was 70.11 (SD = 13.73).

Each participant completed pre- and post-intervention evaluations, which included neuropsychological tests used in the ReCOG neuropsychological evaluation battery built in the third study of this research.

The intervention lasted 10 weeks so that each week there were four group meetings and two individual meetings, consisting of the three programs:

A. *Cognitive Stimulation Program* - 30 group cognitive stimulation sessions (three/week). They lasted 120 minutes. Individual meetings were held weekly, 40-minute meetings with each of the 17 participants.

Each group cognitive stimulation session included three parts:

(a) Space and time orientation exercises: questions about date, time and place, using calendars, clock and posters indicating the place and address where the participants were located

(b) Explanation of the cognitive aspect to be concentrated in each session; with alternatives that include: 1) "memory" (changes that occur with aging, types of memory, strategies such as association and classification); 2) "orientation" (temporal, spatial and personal); 3) "language"; 4) "praxis" (ideomotor and constructive); 5) "calculation"; 6) "perception"; 7) "reasoning"; 8) "attention"; 9) "executive functions" (planning ability, association with activities of everyday life);

(c) Group correction of practical exercises.

The program was adapted to each participant's cognitive abilities. The participants worked five to six different tasks simultaneously, with new tasks introduced periodically, most tasks offered several levels of difficulty, starting with very simple examples and gradually becoming more difficult as the person progressed. In addition, several repetitions were included at each level to give participants the opportunity to practice at any given level. The decision to move a participant to the next level of a given task was determined primarily by the assessment it had at the end of each level.

B. *Lifestyle improvement program* - 10 group physical activity sessions (once/week) and lasted 120 minutes, and the individual weekly ones 40 minutes.

Within this program we focused on two components: the Mediterranean diet and physical activity (physical exercises performed with the physiotherapist).

The Mediterranean diet incorporates various principles of healthy eating that are commonly found in areas near the Mediterranean Sea: increasing consumption of fruit, vegetables, nuts and cereals, replacing butter with healthy fats such as olive oil, limiting the consumption of red meat, using aromatic herbs rather than salt, including fish on the menu at least twice a week.

The FITT model of physical activity provides an easy way to build suitable exercises for people with Alzheimer's disease. The FITT is used to describe the *frequency*, *intensity*, time and the *type* of exercise *used.* This model is recommended in the guides of the English Alzheimer Association and the Alzheimer Association of America.

Below are examples of these different types of group and individual activities.

Dance. Dancing in a sitting position. It increases flexibility, helps maintain a stable balance and can reduce stress.

Exercises performed by sitting on the chair. These exercises are aimed at building or maintaining muscle strength and balance and are less demanding than sitting up exercises. Some examples of seated exercises include: scrolling, rotating the trunk from side to side, lifting the

heels and toes, raising the arms to the ceiling, lifting the opposite arm and leg, imitating cycling, practicing passing from sitting to standing

C. The program to stimulate creativity through acting - 10 group activities (once/week) for a duration of 150 minutes. These were led by an actor and mediated by the psychologist.

The program to stimulate creativity created in this study incorporates techniques of improvisation (changing the end of a story, starting from stories from Romanian folklore) and storytelling of key events in personal life. These techniques emphasize the stimulation of imagination and memory.

Data analysis

Since we had a small sample size, determining the distribution of variables was important for choosing an appropriate statistical method. A Shapiro-Wilk test was therefore performed and the distribution of variables was shown to deviate significantly from normality ($W = 0.26$, p-value < 0.01). Based on this result, a non-parametric Wilcoxon test was used to evaluate pre-and post-intervention differences of the two paired (dependent) groups. This test is recommended for the condition of having the same subjects evaluated twice, pre-and post-intervention comparing score data (Howitt et al., 2010)

The JASP 0.16.2 statistics package was used.

Results

As a result of the intervention strategy, from the results obtained using the Wilcoxon test, statistically significant differences are noted on the tests that measure the global cognitive construct MMSE-2, MoCA, Route A and B test, memory reproduction of the Story, the reverse order number sequence reproduction test (DSB) ($z = -3.621$, $p < .001$), the number sequence reproduction test in the same order (DSF) ($z = -3.296$, $p < .001$) and the replication tests by copying and memory of the Benson figure ($z = -3.180$, $p < .001$).

We have calculated the d-Cohen effect size index, which expresses the size of the comparison effect, to gain a better understanding of the range of benefits related to the intervention. The effect size and 95% confidence intervals were calculated using the difference score (post minus pre-intervention). For non-parametric tests the size of the effect r is calculated as Z divided by the square root of the sample size. The r-value ranges from 0 to nearly 1. The interpretation values for r in the literature are: 0.10 to < 0.3 (small effect), 0.30 to < 0.5 (moderate effect) and >= 0.5 (large effect) (Olejnik and Algina, 2003).

Several covariance analysis were performed to assess pre-and post-intervention differences. Unless otherwise noted, statistical effects associated with $p < .001$ have been reported as significant and effects with η^2 greater than 0.3 (see Table 10).

Table 10. D-Cohen and η^2 Effect Size Indices

T0	M	T1	M	d-Cohen	η^2
MMSE-2	26,52	MMSE-2	28,88	1,77	0.45
MoCA	23,47	MoCA	25,76	2,02	0.52
Storytelling	9,23	Storytelling	16,11	2.12.	0.54
TMTA	44,17	TMTA	34,23	1.25.	0.29
TMTB	133,5	TMTB	113,0	0.75	0.13*
DSF	5.00	DSF	6,29	1,39	0,34
DSB	3,35	DSB	5.00	2,50	0.62
Fig. Benson Copy	14,70	Fig. Benson Copy	14,70	1,45	0,36

Fig. Benson reproduction from memory	9,52	Fig. Benson reproduction from memory	11.11.	1,29	0,30
categorical verbal fluency animals	15,88	categorical verbal fluency animals	20,47	1,73	0.44
categorical verbal fluency vegetables	12,23	categorical verbal fluency vegetables	15,94	1,46	0,36
phonemic verbal fluency letter L	10,94	phonemic verbal fluency letter L	14,64	1,66	0.42
phonemic verbal fluency letter F	9,17	phonemic verbal fluency letter F	13,58	2,44	0.61

Note. $p < .001$, $p < .05$, T0 - pre-intervention scores averages, T1 - post-intervention scores averages, M - mean

Comparison of pre (T0) and post (T1) intervention scores showed large differences at T1 versus T0 in most cognitive assessment tests.

Discussions and conclusions

The current study has shown positive, significant effects of the cognitive stimulation program in individuals with mild cognitive impairment. In general, participants showed an increase in post-intervention cognition.

An important aspect of a successful cognitive stimulation program is its ability to maintain the interest and motivation of participants to such an extent that large amounts of tasks can be accomplished. The current study has achieved a high level of participation.

Individualizing the cognitive stimulation program according to each cognitive domain ensures the success of the therapeutic approach. The involvement of a caregiver could be an important factor in the high completion rate; the diathetic interaction between participants and support staff has most likely facilitated the motivation and effort of participants.

Using improvisational techniques from theatre and storytelling by sharing stories about events and experiences lived at home can provide a way for people with cognitive disorder to express their emotions and socialize with other people in the group in a fun and supportive manner.

The statistical results obtained demonstrate the effectiveness of the intervention through cognitive stimulation programs, improving lifestyle and stimulating creativity.

The limitations of this study are the lack of control and small sample size, the non-homogeneity of the group and the impossibility to introduce the group of people with mild and moderate Alzheimer's disease into the intervention program.

CHAPTER IV. GENERAL DISCUSSIONS: CONCLUSIONS AND IMPLICATIONS

The first objective of the research was to assess cognitive reserve in normal aging older people. In the literature as indicators of CR were proposed: education, premorbid intelligence coefficient (pQI), occupational complexity, and lifelong cognitive activity were used to indirectly estimate an individual's cognitive reserve (Arenaza- Urquijo et al., 2015; Jones et al., 2010).

In the first study, we looked at the relationship between education and cognitive reserve recorded as a total R-IRCq score between (education indicator, occupational complexity and leisure and social activities).

Results from the first study demonstrated that cognitive efficacy was predicted by age (as expected), study level, and total R-IRCq score. An inverse correlation between age and cognitive efficiency has been confirmed: the older the age of participants, the lower the cognitive efficiency, the more significant the correlation when cognitive efficiency is measured using the MoCA cognitive assessment test.

The results confirmed a significant correlation between study level and cognitive efficiency measures, both study level and total cognitive reserve index (R-IRCq) are significant predictors of cognitive efficiency measures. This was also observed by Perneckzy et al. (2006) in a neuroimaging study, in which a higher level of education was associated with a more depleted flux in the parietotemporal area, the location of PET changes in Alzheimer's disease. Perneckzy et al. (2006) found that education altered the association between the pathology of the disease and the levels of cognitive function measured before death. For each additional year of education, the relationship between pathology and cognition was reduced by 0.088 standard units. We can explain this effect of education, perhaps in that formal education is mainly carried out in a critical period of cerebral development.

The assessment of cognitive reserve in older people could be a useful additional measure to integrate existing protocols for the neuropsychological assessment of cognitive decline. It is important to assess this 'threshold effect' where people with a higher level of education may resist the effects of neurodegeneration for a longer period.

Cognitive reserve should also be recognized as a factor that will influence the rate of cognitive decline after diagnosis.

Both cognitive reserve and subjective cognitive decline are closely related to the risk of progression of cognitive decline in dementia.

Given that up to 63% of people aged ≤ 50 years and 74% of people aged ≤ 70 years who achieve normal scores on standard cognitive tests self-report a subjective decline in cognitive functioning (van Harten et al., 2018) is subjective cognitive decline just a feature of normal cognitive aging or should it be recognized as a possible pathological diagnosis?

In recent years, subjective cognitive decline has begun to be considered useful in the diagnosis of prodromal neurocognitive disorders, the 2018 National Institute for Aging - Alzheimer's Association (NIA-AA) research criteria for Alzheimer's disease incorporated CCD as a phase transition between normal cognition and early neurocognitive disorders. Subjective cognitive decline refers to the subjective perception of a decline in cognition (usually in the field of memory) among individuals with normal cognition (i.e. in the absence of objective cognitive deficits).

A personalized diagnostic process could identify or exclude the basic factors of subjective memory complaints, so **the second objective** of this research was to assess the relationship between subjective cognitive decline and cognitive performance. From the results of the second

study, subjective cognitive complaints were found to be closely related to the presence of affective symptoms.

It was also confirmed that **individuals with high anxiety levels are more likely to experience subjective cognitive decline.** This may lead to the uncertainty that subjective cognitive decline, or its correlated anxiety symptoms, could predict further development of neurocognitive disorders. This is particularly relevant given that anxiety has been consistently identified as a key predictor of neurocognitive disorders in several meta-analysis (Santabarbara et al. 2019, Becker et al. 2018).

Most of the study participants had normal scores in the neuropsychological tests, except for 3% who had higher scores (longer pregnancy time, more than 180 seconds) in the Route B test and 15% who had scores below the threshold (less than 15 words/minute) in the categorical verbal fluency (animals) test. These participants also have higher scores on the Anxiety Assessment Questionnaire (DASS-21R). 59% of participants with subjective cognitive complaints had a history of Alzheimer's disease in the family. Anxiety related to the family history of dementia, rather than the real experience of cognitive decline by interpreting memory problems as clinical signs of dementia, may be a reason to present themselves to a specialist control (Buzdugan, 2021).

The role of depressive symptoms in cognitive decline is unclear. The proportion of subjects with mild and moderate depression and threshold scores of the PRMQ questionnaire did not differ significantly from the proportion of subjects in the sample, and the proportion of subjects with mild and moderate depression and threshold scores of the CPSM questionnaire was significantly lower than that of the sample. A study by Perrotin et al. (2017), who studied individuals with subjective cognitive decline in memory clinics and individuals with subjective cognitive decline in a sample of the general population showed a significant reduction in gray matter volume (correlated with AD pathology) in the group of individuals studied in memory clinics. The authors concluded that the need to present themselves at a medical examination and the increase in depressive symptoms were related to the reduction of this volume of gray matter and underlined an increased affective load as a potential part of prodromal AD.

Instead, Heser et al. (2013) found that depressive symptoms were fully mediated by subjective memory impairment concerns, suggesting that depressive symptoms were caused by an increased awareness of subjective decline, explaining the depressive symptom levels of people with subjective cognitive complaints. This last point raises an important point. *Are all people who present with subjective memory complaints to the family doctor always sent to a cognitive evaluation?*

The need for early and differential diagnosis is an important issue in dementia research. Using a battery of concentrated neuropsychological tests can help clarify this image by creating cognitive markers. More specifically, the use of semantic loads, especially semantic fluency loads as a cognitive marker, in differentiating normal aging from Alzheimer's disease is a promising area to investigate. Furthermore, the ability of these pregnancies to identify individuals in a less severe clinical condition than when a diagnosis of AD is made, but who do not appear to age "normally", as seen in the MCI stage, will be of significant clinical importance and a significant goal to reach.

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Study three of this research was conducted to achieve **the third objective**, that of building a battery of neuropsychological tests that can dynamically capture the progression of the disease and its value in the diagnosis of Alzheimer's disease was investigated.

In the third study of this research, it is argued that the diagnosis can be successfully made by deriving performance profiles (cognitive markers) from a series of neuropsychological tests. Establishing performance profiles on neuropsychological tests helps the clinician and researchers achieve greater precision in differentiating normal and abnormal cognitive decline in aging. This approach has implications for diagnostic accuracy but can also be applied to ensure correct interventions (pharmacological and non-pharmacological) in a timely manner to maximize their potential positive effects on patients.

The "ReCOG" neuropsychological test battery was built for the evaluation of several cognitive domains (episodic memory, semantic and working memory, attention, language, visual-spatial abilities and executive functions). Age and education accounted for 5% of the variation in scores on neuropsychological tests.

The last objective of this research was to develop an intervention strategy aimed at improving cognitive deficits, maximizing independence and a possible slowing down of disease progression. The intervention strategy of three programs (cognitive stimulation, lifestyle training and creativity through acting) was used an approach whereby the tasks of each program were developed to influence brain neuroplasticity. The results from study four indicate that the strategy can and has a high potential to improve cognitive deficits. Each participant's post-intervention cognitive performance has increased. The scores obtained in neuropsychological tests differed significantly, confirming the effects of the intervention. The results obtained suggest that running this intervention on a much larger sample will further increase the statistical significance.

Theoretical and conceptual implications

Considering the theoretical analysis and the results obtained in this research we can sketch the neuropsychological profiles (cognitive markers) from the continuum of Alzheimer's disease.

The concepts of *crystallized* and *fluid* intelligence are used to describe models of cognitive change throughout life. Crystallized skills remain stable or gradually improve at a rate of 0.02 to 0.003 standard deviations per year until the sixth and seventh decade of life (Salthouse, 2012). Executive function, processing speed, memory, and psychomotor capacity are considered fluid cognitive domains. Many fluid cognitive abilities, particularly psychomotor skills and processing speed, peak in the third decade of life and decline at an estimated rate of -0.02 standard deviations per year.

Neuropsychological profiles are determined by specific cognitive domains: processing speed, attention, memory, language, visual and spatial abilities, and executive functions.

Processing speed - Many of the cognitive changes reported in healthy older adults are the result of slowing the processing speed. This "slowing down" may have a negative impact on the performance of many neuropsychological tests designed to measure other cognitive domains (e.g. verbal fluency). Thus, a decrease in processing speed can have implications in a variety of cognitive fields. *Attention* - the visible effect of age is observed on more complex attention tasks such as selective and distributive attention. One of the most common cognitive complaints among older adults is *memory* change. Changes in age-related memory are related to slowing down processing speed, reduced ability to ignore irrelevant information (Darowski et al., 2008) and

reduced use of learning and memory improvement strategies (Isingrini and Taconnat, 2008). While decreases in semantic and episodic memory occur with normal aging, the onset of these decreases is different. Episodic memory shows a decrease throughout life, while semantic memory shows a delayed decline (Rönnlund et al., 2005). *Language* is a complex cognitive domain composed of crystallized and fluid cognitive abilities. The overall ability of the language remains intact with aging. It is worth mentioning a few exceptions to the general trend towards stability. The ability to observe a common object and name it, remains roughly the same until the age of 70, and then decreases in subsequent years (Zec et al., 2005). Verbal fluency also shows a decline with aging. *Visual construction skills* decrease over time, unlike visual-spatial skills remain intact. *Executive functions* - Research has shown that concept formation, abstraction capacity and mental flexibility decrease with age, especially after age 70 (Lezak et al., 2012). Aging also affects the ability to inhibit an automatic response in favour of producing a new response. Skills requiring an accelerated motor component are particularly susceptible to the effects of age (Hayden and Welsh-Bohmer, 2011). Other types of executive functions, such as the ability to appreciate similarities, describe the meaning of proverbs, and analyse familiar material, remain stable throughout life.

Clinical and practical implications

Cognitive expression of Alzheimer's disease is closely related to the topography and progression of cerebral neuropathology. Cognitive changes in Alzheimer's disease usually begin with deficits in episodic memory. Memory deficits are the basic problems in mild cognitive disorder (MCI). These memory deficits are not only important for MCI diagnosis, but also because MCI amnestic. However, it is difficult to obtain a universal equation of these memory deficits given the different types of memory-related functions and the diversity of classification prevailing in the literature. Conceptually, for encoding any form of memory, attention is the most important prerequisite. Literature clearly shows that attention shortages are prevalent in the ICM. A direct impact of these attention deficits is on working memory. One of the most common memory deficits encountered in the MCI amnestic is the reduction of episodic memory that has adverse consequences on the functioning of subjects. Prospective memory (MP) is another important cognitive domain that can serve as an early sign of memory decline in mild amnestic cognitive disorder. People with MCI with non-executive syndrome also have poorer verbal memory performance, suggesting a complex interrelationship between memory and executive function. All these cognitive domains are evaluated through a comprehensive neuropsychological battery, which can provide a model of cognitive markers (neuropsychological profiles): useful in early diagnosis, differential diagnosis and even prognosis of disease progression in preclinical stages.

The results of this research highlight the importance of integrating into clinical practice the concept of *continuum* of Alzheimer's disease, the definition of normal cognitive function in older adults, neuropsychological assessment strategies and cognitive interventions with a preventive role in cognitive decline. Cognitive function prediction is strongly dependent on the most accurate determination of preclinical cognitive status and cognitive reserve.

Limitations and future directions for research

This thesis has a few general limitations that must be considered in the interpretation of our results and that can serve as a guide for future research.

Because the first study, that of the assessment of cognitive reserve was a cross-cutting study, we propose as future directions of research:

(1) a longitudinal study indicating the evolution of parameters, R-IRCq education, R-IRC q occupation and R-IRCq leisure activities, their life course and their role in predicting cognitive efficiency and what are the effects of different cognitive reserve on the pathology of Alzheimer's disease.

(2) a longitudinal study assessing the dependence of cognitive decline on the baseline level of cognitive reserve.

A second direction of research is represented by an unaddressed aspect in the literature: on the one hand whether anxiety is only a consequence of subjective cognitive decline, or vice versa, on the other hand, whether subjective cognitive decline and anxiety are both independent predictors of neurocognitive disorders.

The third direction of research will consist in obtaining additional data and analysis on a sample with greater stratification of participants by age groups will be needed to develop normative values of tests in this neuropsychological battery. Also, as a future research direction, we aim to verify the test-test fidelity of the battery and the addition of alternative test variants to eliminate the learning effect. For the comparison of this battery with other neuropsychological test batteries, we consider building a composite battery score, considering the variability of disease expression, and its use in detecting longitudinal changes from early stages of Alzheimer's disease. We propose as future direction of research a study based on running cognitive intervention on three groups (control group, group of people with mild cognitive disorder, group of people with mild and moderate Alzheimer's disease). Also due to the constraints of the pandemic, we only assessed the short-term, immediate effects of the intervention. Future studies will need to include follow-up sessions to assess the effect retention rate and the conversion rate to Alzheimer's disease.

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