ORIGINAL ARTICLE

Psychiatry and Clinical Psychopharmacology 2022;32(4):299-305
DOI:10.5152/pcp.2022.22506

How "Subjective" is Subjective Cognitive Decline?

Alexandru Pavel[1], Valentin Matei[2], Radu Paun[2], Catalina Tudose[2]

[1]Department of Psychiatry, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]Department of Psychiatry, Prof. Dr. Alexandru Obregia Psychiatric Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Background: Subjective cognitive decline is presently considered to be the earliest clinical stage of neurodegeneration. By its current definition, subjective cognitive decline conceptually implies that the sufferer presents no psychometrically measurable cognitive impairment despite numerous articles stating the presence of discrete objective impairments. Our purpose was to evaluate differences in objective cognitive performance in subjective cognitive decline patients compared to healthy controls.
Methods: A total of 101 cognitively unimpaired participants were divided into a subjective cognitive decline group (n = 67) and healthy control group (n = 34). We conducted a thorough cognitive evaluation and collected social, demographic, and clinical data as well as data on personality traits, sleep quality, and physical activity. Both groups were matched for sex, age, education, and Mini-Mental State Examination score.
Results: The subjective cognitive decline group had a lower verbal learning capacity as shown by the worse performance on Rey auditory verbal learning test trial 1 ($P = .021$) and Rey auditory verbal learning test total scores ($P = .023$). The subjective cognitive decline group was significantly more impaired in executive functioning compared to controls, as shown by trail making test A ($P = .012$) evaluation.
Conclusion: Persons with subjective cognitive decline have subtle, objective cognitive impairments which may be undetected with widely used, brief cognitive evaluations, such as the Mini-Mental State Examination. Yet, these impairments are not severe enough to warrant the diagnosis of mild cognitive impairment. Current subjective cognitive decline criteria could be expanded in order to increase the diagnostic precision of subjective cognitive decline.

ARTICLE HISTORY

Received: September 2, 2022
Accepted: November 25, 2022
Publication date: December 30, 2022

INTRODUCTION

Subjective cognitive decline (SCD) has attracted considerable interest in recent years as a potential predictor for more severe cognitive impairment. In 2014, Jessen et al.[1] through the SCD Initiative, developed the research criteria for SCD: "a person's experience of decline in cognitive ability which appears as a modification from a previously 'normal' status which is not related to an acute event." While SCD presupposes the absence of significant objective decline as measured by psychometric tests, previous studies have found that subtle impairments in functional and cognitive performance are present in SCD, with mean test scores within the normal range but lower than that of healthy controls.[2] It is important to include the overall group of SCD participants, both with and without objective impairment in order to appropriately draw conclusions on the meaning of those subtle, objective impairments in the longitudinal prospect of cognitive decline.

Previous studies have recorded such deficits in verbal, visual, and prospective memory that were reliably detected using specialized questionnaires such as the Rey auditory verbal learning test (RAVLT) or the Rey–Osterrieth complex figure test. These impairments are not captured by widely used screening tools such as Mini-Mental State Examination (MMSE) or Montreal cognitive assessment.[3]

It has been postulated that SCD is the link between the preclinical stage of Alzheimer's disease (AD), mild cognitive impairment (MCI), and later dementia, with the limited longitudinal data available suggesting that SCD precedes the diagnosis of dementia by more than 10 years.[4] In a recent systematic review, Parfenov et al[5] showed that people with SCD have a 2.17/2.15 risk of progressing to dementia/MCI compared to control groups. The annual conversion rate to dementia in the SCD group was 1.12% compared to 0.45% in the control group. The annual conversion rate to MCI in the SCD group was 5.44% in the SCD group versus 2.75% in

Corresponding author: Valentin Matei, e-mail: valentin.matei@umfcd.ro

Cite this article as: Pavel A, Matei V, Paun R, Tudose C. How "subjective" is subjective cognitive decline?. *Psychiatry Clin Psychopharmacol*. 2022;32(4):299-305.

the control group. There is evidence that SCD is associated with several biochemical and genetic risk factors commonly related with AD, such as lower concentration of CSF αβ42 and higher ApoE4 frequency.[6] Yet, SCD is a heterogenous condition, and only the longitudinal evaluation can accurately predict which SCD cases will develop dementia.

However, as most individuals with SCD do not suffer further deterioration, there has been continuous effort to find additional clinical and paraclinical factors that would allow the identification of high-risk cases. A significant step in this direction has been the elaboration of the SCD plus criteria[1]: the presence of SCD in the memory domain with onset in the previous 5 years and in persons aged more than 60 years, worries associated with SCD and, if possible, adding confirmation regarding SCD symptoms from a caregiver, and genotyping the ApoE4 status and AD biomarkers. Nonetheless, there is still room for further refining the concept of SCD, perhaps in the form of a classification that reflects the higher risk for MCI and/or dementia in SCD patients with associated objective impairments.

Some of the most common factors that contribute to the heterogeneity of SCD include the co-occurrence or comorbidity of depression or anxiety.[6] Patients who are currently diagnosed with a depressive episode or an anxiety disorder may present with subjective concerns of cognitive decline. Insomnia and use of sleep medication has also been linked to SCD, even when accounting for concomitant depression.[7] Personality traits, mainly neuroticism–anxiety, and the preference for a less active lifestyle may also influence the likelihood to develop SCD.[8]

Increasing attention is being given to cognitive symptoms present in functional cognitive disorders.[9] Functional cognitive disorders represent a group of conditions that usually overlap, in which the person experiences cognitive symptoms in a genuine manner causing distress or disabling the person, but the frequency of the experiences is inconsistent and are not a consequence of somatic disorder.[10] It is still debatable if SCD should be considered a functional cognitive disorder.

MAIN POINTS

- It is believed that subjective cognitive decline (SCD) is a condition in which there is no objective cognitive impairment.
- It has been proven that objective cognitive decline could be present in a certain category of SCD patients but not severe enough to be categorized as having mild cognitive impairment.
- The most significant differences between SCD and controls in our matched (sex, age, education, and Mini-Mental State Examination score) cohort were with regard to attention, memory, and executive functioning.
- Subjective cognitive decline patients have a higher score of negative emotion (BIG 5) trait compared to controls.

Until more light is shed on this topic, it is difficult to say where the place of SCD should be in the current classification manuals ([International Classification of Diseases] ICD-11 and [Diagnostic and Statistical Manual of Mental Disorders] DSM5) or even if it should be categorized as a disorder. It could be argued that it is either a neurocognitive disorder, functional cognitive disorder, or simply the worried well. It is likely that by its current definition, SCD significantly (but not totally) overlaps with all of these categories, hence its heterogenous nature and clinical unwieldiness.

The aim of our study was to conduct an assessment of the cognitive performance in several domains while controlling for any possible confounders such as sociodemographic variables, depression and anxiety disorders, somatic illnesses, personality traits, physical activity and sleep quality in 2 groups of elderly individuals (with SCD and controls). Our hypothesis is that persons with SCD will show slight objective cognitive impairment, enough to differentiate them from healthy controls, yet not severe enough to warrant the diagnosis of MCI/dementia.

To our knowledge, there has not yet been another study of cognitive impairment in SCD to concomitantly account for the above-mentioned moderator factors.

MATERIAL AND METHODS

This study had a cross-sectional design and included patients from a primary care clinic who were recruited after their clinical routine checkup with their general practitioners (GPs).

It was conducted in accordance with the Declaration of Helsinki[11] and has the Ethics Approval from the local IRB (no. 11/06.03.2020). All participants signed an informed consent prior to inclusion.

Inclusion and Exclusion Criteria

The inclusion criteria were: (a) age between 50 and 80 years, (b) MMSE[12] score over 26, (c) Functional Assessment Questionnaire below 9, (d) Hamilton Depression Rating Scale[13] total score below 12,[14] (e) Hamilton Anxiety Rating Scale[15] total score below 17[16], and (f) no substance use in the previous 6 months other than caffeine or tobacco. Exclusion criteria were: (a) diagnosis of major or mild neurocognitive disorder according to DSM5[17] (b) presence of cerebrovascular disease translated as Hachinski[18] score over 4, (c) current diagnosis of neurodevelopment disorder, major depressive disorder, and anxiety disorder according to DSM5, and (d) severe somatic disorders such as epilepsy, organ failure, or other disease that could impair collection of data from the patient such as severe hearing/seeing impairment, and motor deficit. All patients provided informed consent.

Data Collection

We collected social, demographic, and clinical information as well as a comprehensive psychiatric history. History of

somatic and psychiatric illness was evaluated both while interviewing the patient and by screening GP records. Current screening for psychiatric disorders was performed using the Structured Clinical Interview DSM5 Clinician Version.[19] We separately analyzed hypertension and type 2 diabetes since they were the most common somatic diseases present, while other somatic disorders were grouped under "Other." We also presented the patients' medication status for somatic disease as dichotomous variable.

Instruments

Participants were cognitively examined using MMSE,[12] RAVLT,[20] Rey–Osterrieth complex figure test,[21] verbal fluency test (VFT), and trail making test (TMT).[20] We also examined personality traits using Big Five Short Form Questionnaire,[22] the level of physical activity using International Physical Activity Questionnaire (IPAQ),[23] and sleep using Pittsburgh Sleep Quality Index (PSQI),[24] which are some of the possible confounders for SCD. Examinations were performed by 2 trained psychiatrists, and all evaluations were done on a single visit.

Participants were divided into 2 groups: 1 with SCD and 1 without, representing the control group. Subjective cognitive decline was evaluated according to Jessen et al[1] using the question: "Do you feel that you are having difficulties with your memory?" and the possible answers were: "Yes and it bothers me," "Yes but it does not bother me," and "No." Patients that picked any of the answers with "Yes" were categorized as having SCD. This question has been used as the "gold standard" of diagnosing SCD, as can be seen in other studies as well.[5,25,26] At the moment, there are different scales developed for evaluating SCD, but there is no consensus that one of them should replace the current gold standard.

The Hachinski ischemia score[18] is a scale for evaluating the probability that a patient has either vascular dementia, degenerative dementia, or a mixed form. The scale evaluates the timing of cognitive decline, presence of depression, modification in personality, somatic complaints, emotional incontinence, history of hypertension and stroke, evidence of atherosclerosis, and focal neurological signs and symptoms. Each category has a predefined score. A score above 4 increases the likelihood of vascular dementia.

The MMSE[12] is a short test that evaluates attention, memory, calculation, visuospatial ability, and executive functioning. The maximum score is 30, and scores over 24 generally represent lack of cognitive impairment. The Romanian adaptation of MMSE-2 Standard Version[27] presents a cutoff of 25.6 (±1.8) for MCI on a clinical sample of N=221. The mean score for general population sample (N=1407) with ages between 60 and 64 years, with 5-8 years of education, was 24.75 (±3) and for participants with over 16 years of education it was 28.6 (±2.25). The reliability coefficient was $\alpha=0.790$.

The RAVLT (Cronbach's $\alpha=0.801$) consists of a list of 15 words and is designed to evaluate verbal memory. The examinator reads the list, and at the end, the participant is asked to recall as many words as possible. This step is performed 5 times (trials 1-5). The same task is done with a different list of 15 words for a single trial, and then the participant is asked to recall the words from the first list (trial 6). Trial 7 (delay) is done after a 5-minute break, and the patient is asked to recall as many words as possible without reading the list. The last examination of RAVLT (recognition) consists of a text which includes the initial 15 words which patient is asked to recognize.

The Rey–Osterrieth complex figure test (Cronbach's $\alpha=0.810$) consists of 2 trials which examine memory, visuospatial ability, and executive function. In trial 1 (Rey copying), the patient is asked to copy a complex figure. After a 3-minute break, the patient is asked to draw the figure from his memory. The maximum score is 36.

The VFT (Cronbach's $\alpha=0.871$) test examines verbal ability and executive function of the patient. We used the letter fluency type, which consists in 3 trials of 1 minute each in which the patient has to tell the clinician as many words as possible to begin with a given letter. The same letters were given in the same order for all patients. The patient is asked not to proper names, not to repeat the same words, and not to use derivatives/diminutives of a single word (e.g., bird and birdy). In our analysis, we summed all the correct words from all 3 trials into a single score (VFT total).

The TMT (Cronbach's $\alpha=0.749$) examines a variety of cognitive functions such as attention, visual and spatial ability, sequencing and shifting, psychomotor speed, abstraction, flexibility, and executive function.[20] It is a time-dependent examination with 2 tasks: one (TMT A) where the patient has to connect numbers consecutively (e.g., 1-2-3) and the second part (TMT B) where the patient has to connect both numbers and letters (e.g., 1-A-2-B). The cutoff for trial A is considered 78 seconds and for trial B 273 seconds.[28]

The Big Five Short Version (Cronbach's $\alpha=0.683$) is a questionnaire that evaluates personality across 5 domains: extraversion, agreeableness, conscientiousness, negative emotionality, and open-mindedness. It consists of 30 items, each scored from 1 to 5 on a Likert scale. Continuous scores are computed according to scoring instructions for each domain.

The IPAQ (Cronbach's $\alpha=0.520$) evaluates health-related physical activity performed in the last week, across 4 domains: leisure-related physical activity, domestic and gardening (yard) activities, work-related physical activity, and transport-related physical activity. Scores for each domain are calculated in multiples of resting metabolic

rates (METs) performed for minutes (MET-minutes). A total score is computed by adding the scores of each domain.

The PSQI (Cronbach's $\alpha = 0.709$) is a self-administered questionnaire that examines sleep quality over the last month. It evaluates sleep quality across 7 domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The global score is obtained by summing scores from each domain. Patients with total scores over 5 are considered to have poor sleep quality.

Subjective cognitive decline is an extremely heterogenous condition; thus, power analysis based solely on prevalence is difficult to appreciate. Using the anticipated mean calculations, if we input a 2-point difference between controls and the SCD group, 90% power, and an alpha value of 0.05, the results returned a group size of 42. We also evaluated other cross-sectional studies evaluating SCD and determined that a sample size close to 100 participants in total should be powerful enough to warrant statistical significance.[29,30]

Statistical Analysis

All the analyses were performed using Statistical Package for the Social Science Statistics v26 (IBM SPSS Corp., Armonk, NY, USA). We used the matching algorithm of the program on sex, age, and education variables for the 2 groups. Descriptive statistics were used to characterize the sample. We used Chi-square test to analyze categorical variables such as gender, locative status, presence of hypertension or type 2 diabetes. We used Shapiro–Wilk test to assess the normality of data and established that variables with significance over 0.05 were normally distributed; otherwise, it was considered non-normally distributed. We used the Student's *t*-test (for normally distributed data) or Mann–Whitney *U* test (in cases where the data do not conform to the normal distribution) to analyze continuous data such as age, education, and scores for the applied questionnaires. Subjective cognitive decline and control groups were matched for education and age. Categorical data were presented with number of participants (%), while continuous data were presented as mean (SD) for normally distributed data and median (interquartile range) for non-parametric data. Statistical significance was defined as *P* below .05, 2-sided.

RESULTS

There were 110 patients who signed informed consent. After matching for sex, age, education, and MMSE score, a total of n = 101 patients were included in the final analysis—67 (66.33%) with SCD and 34 (33.66%) controls. Social, demographic, and clinical characteristics are presented in Table 1. There were no statistically significant differences between SCD and the control group regarding sociodemographic and clinical characteristics. More participants from the SCD group had a history of depression (*P* = .043), but none of the participants were depressed at the time of inclusion. Also, the negative emotion trait of Big Five was significantly more present in the SCD group (*P* = .043).

Table 1. Sociodemographic and Clinical Characteristics of the Groups

Item	SCD (n = 67)	Control (n = 34)	*P*
Gender (female)	50 (74.6%)	21 (61.8%)	.181
Age			
Median (IQR)	63 (56-69)	59.5 (52-67)	.052
Education (years)*			
Median (IQR)	13 (12-16)	15 (12-17)	.213
From urban area	42 (62.7%)	22 (64.7%)	.842
Living with another person	40 (59.7%)	29 (85.3%)	.009
Smoking (packages/year)	0	0 (0-1.75)	.452
Alcohol (g/day)	0	0	.253
BMI*			
Median (IQR)	27.55 (24.22-32.02)	24.69 (24.56-30.54)	.558
Hypertension	35 (52.2%)	13 (38.2%)	.183
Type 2 diabetes	12 (17.9%)	4 (11.8%)	.424
Other somatic disorders	23 (34.3%)	7 (20.6%)	.153
Currently on treatment for somatic disorders	44 (65.7%)	16 (47.1%)	.072
Hachinski score			
Median (IQR)	2 (1-2)	2 (1-2)	.059
History of depression	20 (33.3%)	4 (13.3%)	**.044**
FAQ*			
Median (IQR)	2 (1-2)	2 (1-2)	.590
HAMD*			
Median (IQR)	1 (0-3)	1 (0-3)	.915
HAMA*			
Median (IQR)	2 (0-4)	2 (0-5)	.982
BIG5			
Extraversion	17.25 (±4.41)	17.85 (±3.36)	.488
Agreeableness	19.37 (±2.92)	19.18 (±3.05)	.753
Conscientiousness*	21 (18-25)	21 (19.75-24)	.971
Negative emotion	14.37 (±4.15)	12.64 (±3.68)	**.043**
Open-mindedness	17.46 (±4.39)	17.21 (±4.24)	.779
IPAQ total*	3600 (1386-6300)	3093.5 (1690-6264)	.917
PSQI*	5 (3-8)	4 (2.75-7)	.438

BMI, body mass index; FAQ, Functional Assessment Questionnaire; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Rating Scale; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; PSQI, Pittsburgh Sleep Quality Index; SCD, subjective cognitive decline.
Data presented in bold reached statistical significance or trend; items presented with * were analyzed with Mann–Whitney and presented with median (IQR).

Table 2. Cognitive Evaluation of Participants

Item	SCD (n=67)	Control (n=34)	*P*
MMSE*			
Median (IQR)	29 (27-30)	29 (28-30)	.162
RAVLT Trial 1*			
Median (IQR)	4 (3-6)	5 (4-6)	**.021**
RAVLT Trial 5*			
Median (IQR)	9 (7-12)	11 (9-13)	.073
RAVLT total	37.16 (±10.75)	42.44 (±11.16)	**.023**
RAVLT Trial 6	7.85 (±3.18)	8.94 (±3.28)	.110
RAVLT delay	7.57 (±3.10)	8.47 (±3.70)	.198
RAVLT recognition*			
Median (IQR)	14 (12-15)	14 (12-15)	.950
Rey copying*			
Median (IQR)	36 (34-36)	36 (34-36)	.917
Rey memory*			
Median (IQR)	20 (14-27)	22.75 (12.75-29.25)	.439
TMT A*	56 (46-88)	47 (40.75-59.25)	**.012**
Median (IQR)			
TMT B*			
Median (IQR)	131 (97-194)	113 (82.25-173.25)	.138
VFT total	31.93 (±12.48)	33.97 (±11.06)	.421

IQR, interquartile range; MMSE, Mini-Mental State Examination; RAVLT, Rey auditory verbal learning test; TMT, trail making test; VFT, verbal fluency test.
Data in bold reached statistical significance or trend; items presented with * were analyzed with Mann–Whitney and presented with median (IQR).

The cognitive evaluation scores are presented in Table 2. Patients with SCD performed significantly worse on RAVLT trial 1 ($P=.021$) and RAVLT total ($P=.023$). There was also a significantly poorer performance on the TMT A test in the SCD group ($P=.012$).

DISCUSSION

We found that subjects with SCD performed worse than controls in the RAVLT, which measures the ability to encode, combine, store, and recover verbal information in different stages of immediate memory.[20] They performed significantly worse than controls in the first trial of the test, which evaluates the attention and immediate recall, resulting in a lower final score, but did not score significantly lower in the following 4 trials, which also evaluate attention and immediate to short-term memory, thus managing to increase their focus after the first trial. No difference between the 2 groups was found in the delayed recall and recognition tests. A potential explanation for the score differences on the RAVLT is that SCD may be associated with small but significant impairments in voluntary attention, anticipating the more severe deficits found in objective cognitive decline.[30] It may be that SCD patients could represent the lower end of the "healthy" cognitive functioning continuum, corresponding to a smaller cognitive reserve, and higher probability to develop a major neurocognitive disorder later in life. It is also possible that these initial changes in cognition could represent the starting point of a neurodegenerative process. Another explanation could relate to performance anxiety in the SCD group; more precisely, they may perceive increased pressure to perform on the first trial due to their subjective feeling of cognitive decline (cognitive bias), which may interfere with sustained attention. This would also partially explain the non-significant differences in scores from next trials of RAVLT, as repetition may help overcome initial anxiety. A similar pattern emerged in the TMT, which evaluates visual attention and task switching. As in the RAVLT, intergroup differences were present in TMT A but not in the more complex TMT B, possibly reflecting that individuals managed to better control their anxiety and perform better in TMT B compared to TMT A.

We found that persons with SCD have increased expression of the negative emotionality personality trait. Generally, persons with higher negative emotionality experience, in general, anxiety, grief, and sadness more frequently and intensely compared to persons with lower levels of negative emotionality.[31] By accounting for the presence of clinically significant anxiety and depressive disorders in our study population, we have removed some of the potential confounding effect they might have had on cognitive functioning. There is difficulty to establish the directionality of the causal chain in these situations; we cannot say if anxious traits were present before the subjective cognitive symptoms or after persons started noticing their symptoms, thus being the response of a person with increased neuroticism to a perceived cognitive impairment. This represents an important point in SCD research because one of the main predictors for future, objective cognitive decline in SCD persons is the presence of anxiety.[32]

Another explanation for this phenomenon is metacognitive error. Metacognition is defined as an ability to think about thinking; thus a discordance between subjective reports of memory complaints and actual performance could represent a metacognitive error. For example, Chin et al[33] found an association between SCD and increased self-focus attention. This could also be one of the reasons why SCD has a slightly worse objective performance compared to controls.

We have found no statistically significant differences in tests in which attention is not the main focus, such as the VFT or Rey-Osterreith complex figure test. This can be seen as supporting our previous inference that patients with SCD have some initial difficulties focusing on attention intensive tasks which are alleviated by repetition.

One-third of the SCD group had a history of depressive episodes compared to approximately one-seventh of the control group. It is known that in persons with major depressive disorder, cognitive deficits such as impairment of attention, learning and memory, and working memory may persist even after the patient has achieved clinical remission.[34]

In order to eliminate cognitive dysfunction associated with depression, which may represent a confounding factor, we excluded participants with current depressive episodes. We included persons with history of depression because it is a known risk factor for cognitive decline. We cannot exclude the possibility that a subgroup of the SCD participants with a history of depression might actually represent trait impairment of cognitive functioning in presently euthymic state.

Our results are in line with the current literature which is uncertain regarding the meaning of objective cognitive decline in SCD. McWhirter et al's[9] systematic review found that 18 out of 32 studies stated a positive association between subjective cognitive symptoms and objective impairment. This argues the heterogeneity of the SCD concept where not all persons who express SCD also have subtle, objective cognitive impairment, warranting longitudinal studies in order to stratify the risk of developing MCI/dementia both in SCD persons with objective impairment and in SCD persons without objective impairment.

Our study suggests that the present criteria used to diagnose SCD could be expanded to increase its sensitivity for predicting further cognitive decline. We are not aware of any other study that differentiates between these 2 conditions (SCD with subtle objective cognitive impairment and without any objective impairment). Studying the differences between these sub-types may clarify the transition from normal cognition to SCD without objective cognitive impairments, to SCD with subtle objective cognitive impairments, and, possibly, to MCI and dementia.

The main limitations of our study are the cross-sectional design and the relatively small number of subjects included. As most cases of SCD remain stationary, a longitudinal evaluation would be more suitable to identify parameters associated with higher risk of progression. The lack of data regarding biomarkers could also be considered a limitation. There are studies which state that the presence of biomarkers (ApoE4 profile or high levels of CSF amyloid) in SCD individuals increases the risk of future cognitive decline.[35]

Our principal strengths are the psychometric evaluation of depression, anxiety, and personality traits, as well as the assessment of sleep quality, physical activity, several common somatic illnesses, and treatment adherence to them, all of which can be important confounding factors when evaluating cognitive performance in the elderly. All these possible confounders were controlled.

In conclusion, cases with SCD (as currently defined) may be associated with difficulties in verbal and visual memory-related tasks that are not registered by commonly used screening instruments such as the MMSE. Further studies are necessary to determine the longitudinal evolution of these 2 different groups, SCD with and without discrete objective cognitive impairment, their relevance as predictors of further progression, and whether additional cognitive functioning criteria are necessary.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Romanian Alzheimer Society (Approval No: 11/06.03.2020).

Informed Consent: Informed consent was obtained from all patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.P., V.M., R.P.; Design - A.P., V.M., C.T.; Supervision - V.M., R.P., C.T.; Materials - A.P.; Data Collection and/or Processing - A.P.; Analysis and/or Interpretation - A.P., V.M., R.P.; Literature Review - A.P., R.P.; Writing - A.P., V.M., R.P., C.T.; Critical Review - A.P., V.M., R.P., C.T.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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