Cerebral Circulation - Cognition and Behavior 5 (2023) 100186

Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior

The relevance of the socio-emotional deficits in cerebral small vessels disease (CSVD): An exploratory study with sporadic CSVD and CADASIL patients

Ana Rita Silva [a,*], Irina Santos [b], Carolina Fernandes [c], Cristiana Silva [c], Daniela Pereira [d], Orlando Galego [d], Henrique Queiroz [d], Maria do Rosário Almeida [e], Inês Baldeiras [f], Gustavo Santo [c]

[a] CINEICC – Center for Research in Neuropsychology and Cognitive Behavioral Interventions of the University of Coimbra, Colegio Novo Street, N/A, Coimbra 3000-115, Portugal
[b] Neurology Department, Academic and Clinical Centre – Coimbra University Hospitals, Coimbra, Portugal
[c] Department of Neurology, Centro Hospitalar e Universitário de Coimbra, CNC-CIBB, Coimbra, Portugal
[d] Neurorradiology Functional Unit, Coimbra University Hospitals, Coimbra, Portugal
[e] Center for Neurosciences and Cell Biology, CNC, University of Coimbra, Coimbra, Portugal
[f] Faculty of Medicine of the University of Coimbra, Coimbra, Portugal

ARTICLE INFO

Keywords:
Cerebral small vessels disease (CSVD)
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Neuropsychological changes
Socio-emotional profile
Cognitive impairment
Emotion regulation

STRUCTURED ABSTRACT

Background: Cerebral Small Vessels Disease (CSVD) is categorized in different forms, the most common being the sporadic form and a genetic variant – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). Amongst the most frequent clinical manifestations are the neuropsychological changes of cognitive, behavioral, and emotional nature, whose features are still under debate.
Objective: This exploratory study aimed to compare the neuropsychological profile of a sporadic CSVD sample and a CADASIL sample with an age, education, and gender matched control group, between the ages of 30–65 YO (total sample mean age=51.16; SD=4.31).
Methods: 20 patients with sporadic CSVD, 20 patients with CADASIL and 20 matched controls completed a neuropsychological assessment battery. Global cognitive state, processing speed, working memory, attention, executive dysfunction, episodic memory, social cognition, impulsivity, apathy, alexithymia, depression, and anxiety were measured. White matter hyperintensities (WMH) volume were quantified and measured as lesion burden.
Results: The cognitive differences found between the clinical groups combined (after confirming no differences between the two clinical groups) and matched controls were restricted to speed processing scores ($d = 0.32$ 95 % CI [.12-.47]). The socio-emotional and behavioral profile revealed significantly higher levels of depression ($d = 0.21$, 95 % CI [.16-.33]). and anxiety ($d = 0.25$ 95 % CI [.19-.32]) in CADASIL and sporadic CSVD groups, and the same for the alexithymia score ($d = 0.533$ 95 % CI [.32-.65]) were the clinical groups revealed impoverished emotional processing compared to controls. WMH only significantly correlated with the cognitive changes and age.
Conclusions: In our study, CADASIL and sporadic cSVD patients combined, present multiple emotional-behavioral symptoms - alexithymia, anxiety, depression, and in a lower extent apathy and impulsivity – suggesting for the presence of emotion dysregulation behaviors, present independently of age and of the presence of cognitive deficits. Despite of the small sample size that could underpower some findings, this exploratory research supported that these symptoms may have a significant impact in disease monitoring, progression, and prognosis, requiring further investigation regarding their neurophysiological substrates.

* Corresponding author.
E-mail address: anaritaess@fpce.uc.pt (A.R. Silva).

https://doi.org/10.1016/j.cccb.2023.100186
Received 19 April 2023; Received in revised form 3 September 2023; Accepted 25 September 2023
Available online 27 September 2023

1. Introduction

Cerebral Small Vessel Disease (cSVD) includes a group of pathological events that affects small arteries, arterioles, capillaries and venulas of the brain. cSVD are categorized in different forms, the most common being the sporadic form. Inheritable or genetic risk factors are estimated to account for approximately 20 % of cSVD cases [1]. Amongst the genetic variants, the most common is the *Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy* (CADASIL). Its prevalence is higher as people age, but is not restricted to older adults, with its onset occurring for the third/fourth decade of life, especially in the genetic forms [2,3]. CADASIL is a monogenic autosomal dominant disorder caused by mutations in NOTCH3 gene.

Early life factors such as vascular risk factors and child and adult poor socioeconomic status, as well as low education and cognitive reserve are independently described to contribute to worse clinical onset of cSVD [4].

Clinical manifestations are subtle, may be expressed as migraine with aura, early cerebrovascular mild events. Neuropsychological manifestations are also common, but very subtle in the early phases of the disease, and with a relatively slow progression profile [5,6]. The latest are mainly of cognitive and emotional nature, including various levels of cognitive decline, mood, and behavioral disorders. Scientific data points apathy and depression as the most prevalent behavioral and emotional alterations; regarding neurocognitive changes, there are highlighted a decrease in speed processing, executive dysfunction and memory retrieval deficits, in both types of cSVD, several times associated with the emotional changes described [7,8].

The presence of this triad of cognitive, emotional, and behavioral symptoms, are phenotypic traits of CADASIL, but have also been demonstrated for the sporadic cSVD [9,10]. Emotional symptoms such as depression (mainly mild to moderate symptoms of depression), have been described as a key feature of CADASIL [8,11], and several case reports have pointed for the hypothesis that emotional disturbance may occur prior to any other cognitive symptoms [12], requiring an adequate psychiatric monitoring. [13] Depressive symptoms have recently been associated with poor perceived quality of life on both genetic and sporadic forms of cSVD [8]. This highlights the relevance to look in depth to the intersection between emotional, cognitive, and behavioral symptoms early in the course of the disease, for adequate prevention of its negative impact in individuals' daily activities [12].

Symptoms' description in literature regarding behavior change is scarse, except for apathy, described as the most prevalent behavioral condition in cSVD [14]. Apathy is particularly frequent after a first stroke, but it is also present in patients without stroke, and even in subclinical sSVD., named "vascular apathy" [12,15,16] Other symptoms described in case series or case reports point out for irritability, anger, and higher impulsivity as other significant behavioral changes in these patients [15].

Both emotional and behavioral changes have been recently researched in terms of their neurophysiological correlates. In this matter, the level of white matter damage has been associated with mood changes, particularly depression. [17] Apathy in CADASIL patient has recently been associated with a reduced cortical surface and with morphological changes in medial-frontal and orbitofrontal cortex [18], as well as with a reduced fractional anisotropy in brain networks associated with effort-based decisions [16]. With patients with sporadic cSVD, apathy but not depression was associated with damage in cortico-subcortical networks associated with emotion regulation, reward, and goal-driven behavior [19,20]. Nevertheless, it is not clear whether emotional and behavioral symptoms are association with cSVD lesion load, similarly to what was found for cognitive symptoms [21,22].

The fact that mood and behavioral changes demonstrated to be some of the more relevant symptoms at the disease clinical identification [11, 12], this led Kan and colleagues to look for the impact of these symptoms during cSVD progression, concluding that a higher level of neuropsychiatric symptomatology (measured by the Neuropsychiatric Inventory administered to a relative) early in the disease is associated with worse clinical evolution and with cognitive decline over 2 years [23].

With the above background, it is clear the importance of behavior and emotional disturbance in the early phases of cSVD and the impact these changes may have, but most studies regarding these alterations looked into just a few number of emotional and behavioral symptoms, or relied in informant based measures to analyze emotional symptomatology, measures that, when taken alone are less robust in comparison than the current proposed protocol [8]. Additionally, despite some case reports, variables such as emotion regulation, emotion recognition (e.g. alexithymia - characterized by an impaired ability to be aware of, explicitly identify, and describe one's expressed emotions or feelings) [24] and impulsivity [15,25,26] have not been analyzed in larger samples, or they only examined older individuals [27]. Finally, a cognitive dimension that may be correlated significantly to emotional and behavioral deficits, such as social cognition [28], was never tested yet in these populations. Social cognition is described as a domain than enables people to perceive, remember and use emotional and interpersonal information to explain and/predict their own behavior and the others. As such, this cognitive domain should be addressed as part of the understanding of the cognitive and non-cognitive symptoms present in cSVD, [29] Neuroimaging data points for the presence of poor function in certain brain regions and networks that may compromise behavior, social, and emotional functioning. With a more comprehensive examination of these variables, one could elicit some more detailed neuropsychological profile of these patients and contribute for an adequate monitoring and treatment of these impactful symptoms.

1.1. Study objectives

The present case-control study aims to explore in depth the neuropsychological profile of individuals with cSVD, both examining patients with sporadic cSVD and CADASIL, matched by age, gender, and educational status and compared with an age, gender, and education matched group of healthy controls. With these groups matched for relevant socio-demographic variables, we aim to understand in more detail the type of mood, behavior and cognitive changes, and the correlations between them. We additionally aim to explore the relationship between disease severity (measured by magnetic resonance imaging - MRI of white matter hyperintensities volume – MRI WMH volume), socio-demographic profile and both cognitive, emotional, and behavioral symptoms in both cSVD groups. This exploratory study intends to offer future studies a more complete comprehensive protocol for better monitoring impairment in emotion and behavior function.

2. Materials and methods

2.1. Sample

2.1.1. Study population 1: CADASIL

The CADASIL sample was collected in the Neurology Service of the Hospital and University Center of Coimbra. The patients were consecutively selected from a cohort of CADASIL patients regularly followed un in the cerebrovascular risk consultation. At this consultation, patients were monitored with several periodic diagnostic tests, such as biological samples and cerebral MRI. The inclusion criteria consisted of: (i) a previous clinical diagnosis of CADASIL, confirmed by genetic testing, and (ii) age below 66 years old; (iii) a cerebral MRI routinely performed in the previous 12 months with quantification of WMH load. CADASIL diagnostic criteria was considered in the presence of clinical (either recurrent small subcortical infarctions, migraine, gait disturbances, psychiatric disturbances, or cognitive decline), imagiological features typical of CADASIL [30] and the identification of pathogenic NOTCH3 variants by molecular analysis, either by Sanger sequencing or

NGS-customized gene panel. [31]Exclusion criteria included: (i) presence of dementia (above the cutoff for dementia described by the Portuguese norms [32], and according to the clinical criteria from International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), the diagnostic criteria proposed by the National Institute on Aging–Alzheimer's Association Workgroup (NIA-AA), and Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (ii) significant changes in visual or auditory acuity that could compromise the performance of the assessment; (iii) unstable clinical status (e.g. delirium, etc.).

2.1.2. Study population 2: sporadic cSVD

The sporadic cSVD sample was equally collected in the same clinical context of the CADASIL sample. The inclusion criteria consisted of (i) a previous diagnosis of sporadic cSVD; (ii) age below 66 years old; (iii) a cerebral MRI routinely performed in the previous 12 months with quantification of WMH load. cSVD was defined as a group of pathological processes with various aetiologies that affect the small arteries, arterioles, venules, and capillaries of the brain. In the consultation, cSVD patients are integrated after the identification of brain lesion of presumed vascular ethiology (commonly performance after a migraine episode or incidentally discovered) whose volume is considered disproportionate to the patients vascular risk factors. According to the aetiopathogenic classification of cSVD [33], the following criteria was used to consider sporadic cSVD: (i) patients with white matter lesions (subcortical or periventricular) of presumed vascular origin; (ii) absence of clinical or radiological biomarkers of cerebral amyloid angiopathy; (iii) exclusion of the most prevalent causes of inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy by performing cSVD Next Generation Sequencing (NGS) panel (7 genes: TREX1, COL4A1, COL4A2, GLA, NOTCH3, HTRA1, CTC1); iv) exclusion of inflammatory and immunologically mediated small vessel diseases. The exclusion criteria were the same as the one for the CADASIL sample.

2.1.3. Study population 3: matched healthy controls

The matched healthy controls were selected among healthy volunteers that participate in studies from our Academic Clinical centre database, and who have performed recent brain MRI that considered no to have any cerebral lesions such as those of presumed vascular etiology. The inclusion criteria consisted of (i) age below 66 years old; (ii) gender and educational level matching sporadic CSVD and CADASIL groups (this group data was collected after the clinical groups data collection). The exclusion criteria were (i) the presence of cognitive impairment, as measured by MoCA (cut-off variable according to Portuguese normative data, established according to age and educational status) [34]; (ii) history of brain trauma or cerebrovascular events; (iii) significant changes in visual and auditory acuity that could compromise neuropsychological assessment. Given the lack of sufficient matched sample with the required criteria, the control group was not matched for the most important vascular risk factors.

All subjects gave written informed consents. The study was submitted to the Ethics Committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra (CEDI/FPCEUC:78/12) and was carried out following the Declaration of Helsinki.

2.2. Procedures

2.2.1. Assessment measures

All the participants were assessed using a comprehensive neuropsychological battery, comprising instruments that evaluate their cognitive and social-emotional state. All tests were administered by experienced professionals and clinical psychology trainees with supervision. Each session of neuropsychological assessment lasted approximately 1h30. The time frame for assessment between the clinical groups was the same, whereas the control group assessment was performed after the conclusion of the clinical groups assessment, to match for age and years of education

2.2.1.1. Montreal cognitive assessment (MoCA). The MoCA is a brief cognitive assessment instrument, originally developed as a screening test for the slightest forms of cognitive decline. It evaluates the Executive Function, the Visuospatial Ability, Memory, Attention, Concentration and Working Memory, Language and Orientation (temporal and spatial) [34]

2.2.1.2. Digit symbol coding test – weschler scale. The Digit Symbol Coding Test is a subtest of the Wechsler Adult Intelligence Scale (WAIS-III) and assesses the processing speed, working memory and attention. Its score equals the number of symbols correctly reproduced in the time limit of 120 s. [35]

2.2.1.3. Month ordering test. The Month Ordering Test assesses the working memory. It is composed of 5 difficulty levels that increase progressively and each level has 4 trials [36].

2.2.1.4. Frontal assessment battery (FAB). The FAB is a screening battery that evaluates abstract thinking, mental flexibility, motor programming, sensitivity to interference, inhibiting control and independence of the environment, functions controlled by the frontal lobe. This instrument is frequently used to detect executive dysfunction [37].

2.2.1.5. Verbal fluency task. The Verbal Fluency Task is composed of the phonemic and semantic verbal fluency tasks, that assess the non-motor processing speed, executive functions, and language production [38].

2.2.1.6. Free and cued selective reminding test – word version (FCSRT). The FCSRT is a learning and verbal memory test, which consists of learning and recalling words that are previously associated with semantic categories. The instrument is composed of 16 words that are associated with their respective semantic categories. There are 3 trials, separated by a distractive task [39].

2.2.1.7. Reading the mind in the eyes (RMTE). The RMTE test is a facial perception task that assesses the patient's social cognition. Patients must associate pictures of strangers' faces to a certain mental state, within four options [40].

2.2.1.8. Barratt impulsivity scale (BIS-11). The BIS-11 evaluates impulsivity. It's a self-report scale, composed of 30 items, classified according to a Likert scale of 4 points ([1–4]). A higher result is associated with higher levels of impulsivity [41].

2.2.1.9. Toronto alexithymia scale (TAS-20). The TAS-20 is a self-report questionnaire with 30 items aimed to identify an individual's difficulty in identify and describe emotions and/or a tendency to minimize emotional experiences. A higher score corresponds to higher levels of alexithymia [42].

2.2.1.10. Apathy scale (AS). The AS has the purpose to identify and quantify apathy. Higher results correspond to higher levels of apathy [43].

2.2.1.11. Hospital anxiety and depression scale (HADS). The HADS is a screening scale to identify anxiety and depression in a hospital environment. This test consists of two scales, one that assesses anxiety, and the other evaluates depression. Higher results demonstrate the presence and severity of the symptom [44].

2.2.2. Lesion volume quantification

Participants from the clinical groups were assessed with a MRI, all being scanned on the same MRI Scanner. A standardized 3.0 Tesla MRI protocol on a 3.0T Siemens Magnetom Trio scanner (Erlangen, Germany) and using a 32-channel head antenna was implemented, including 3D T1-weighted, 3D FLAIR, 3D T2-weighted sequences. The WMH volume was determined using the 3D Slicer software (v4.10.2, freely available at [1]). A semiautomatic segmentation was performed by one experienced neuroradiologist using the 3D FLAIR images. For this determination, the hyperintense white matter lesions were all manually contoured, with the process being facilitated by the automatic recognition of neighboring voxels with similar intensity and, further, their total volume calculated with the software's automatic segmentation statistics tool (total voxel volume, with the Labelmap Statistics plugin). Thus, total volume of white matter lesions did not include: ischemic infarcts with territorial pattern, lacunar infarcts in basal ganglia, lacunar white matter infarcts with cavitation (that is, hypointense in FLAIR). Additionally, a Fazekas score was determined by the neuroradiologist according to the original stablished norms [45].

2.2.3. Data completeness

In the three groups, all assessment measures data were available for all participants with exception to the TAS-20, who was available for only 17 participants of the CADASIL group, 18 participants for the sporadic CSVD group and 15 participants of the healthy control group. 2 participants from the sporadic CSVD group did not complete the BIS-11 questionnaires. All additional measures data were completed.

2.2.4. Statistical analysis

Prior to analysis, variables were plotted, and normality of distribution was confirmed by the Kolmogorov-Smirnov test. Given that groups were expected to be matched for age, gender, and educational level, we performed analyses of variance and Chi-square test to confirm the absence of differences prior to the remaining analyses. To correct for multiple comparisons, the significance level for group differences was adjusted for the number of tests using the Bonferroni-Holm correction ($p<.00625$ for cognitive tests and $p<.00714$ for the socio-emotional measures). One-way ANOVAs were used to compare the CADASIL group, the sporadic CSVD group and the control group, in all administered scales raw/unadjusted scores. Post-hoc comparisons were performed using Bonferroni post hoc test for statistical differences. To handle for missing data, giving the small number of missing values, we input mean values to the null entries for the two variables including missing data. Raw test scores were transformed into z-scores so that we were able to compare groups' performance in the different domains of functioning without regard to the employed test procedures. First, we calculated the mean and standard deviation for each measure for all the groups combined (the pooled sample), Second, we calculated a z-score for each participant (the formula is $z= (X-M)/SD$, where X is the raw score, and M and SD are the values estimated in the first step). Positive z scores indicate a result that is above the mean of the pooled sample, and negative z scores indicate a result that is below the pooled mean. For having a global estimation of the differences of the three groups, composite scores combining the z-scores were stablished, and z-scores were averaged. In this way, it is possible to compare the average standardized score between the three groups and offer a clearer understanding of their profile. This method was performed due to the lack of Portuguese normative data for most of the measures included in the protocol.

The two clinical groups were grouped as a single clinical sample in order examine the relationship between relevant variables, using first correlation analyses and consequently simple linear regression analyses for the outcomes significantly correlated with lesion load, to calculate coefficients of determination (R^2).

IBM SPSS Statistics 27.0 software was used for all statistical analysis.

3. Results

3.1. Descriptives

The demographics and global clinical status of the three study groups are described in Table 1.

Regarding group differences concerning global demographic and clinical profile, as expected no differences were found for age (z [2]= 2.43, p=.098), educational level (z [2]=1.05, p=.359), gender (χ2 [2]= 2.57, p=.276) or global cognitive status as measured with the MoCA (z [2]=1.89, p=.171). However, when stratifying groups by age groups, differences were found ((χ2 [2]=16.9, p=.01), with the healthy control group presenting less participants between 61 and 65 years old comparatively with the clinical groups. Additionally, they were found significant differences in the lesion load for the clinical groups. Using an independent sample t-test, we found that the CADASIL group presented significantly higher level of WMH lesion burden comparatively with the sporadic CSVD group, either looking at the Fazekas score (t [38]=3.45, p=.002) or to the total lesion volume score (t [38]=2.64, p=.014). Regarding vascular risk factors, hypertension and diabetes were more prevalent in CADASIL and sporadic cSVD groups (55 % and 45 %, respectively) compared to controls (10 %), and migraine was more prevalent in cSVD group (55 %) (Table 2).

Values are number (%) or mean (SD) as appropriate.

3.2. Main results

3.2.1. Neuropsychological outcomes compared with a matched healthy population

Regarding the cognitive profile of the groups observing the raw/unadjusted test scores, and after correcting for multiple comparisons, only one difference in the digit symbol coding score between the three groups were found (F (57)=11.897, p=.001). Post hoc comparisons using the Bonferroni test indicated that the mean score for the control group (Mean= 68.28, SD=12.52) was significantly higher than for the CADASIL group (Mean=44.22, SD=23.93, p=.0001) and the sporadic CSVD group (Mean=38.72, SD=19.13, p=.0001), with these two groups not differing between them (p = 1.00).

Relatively to the measures of socio-emotional status, observing its raw/unadjusted scores, despite of the presence of a set of measures with statistical differences to the level of p=.05 using Bonferroni correction significance level we found only statistically significant differences in the HADS, in the HADS anxiety score and in the TAS-20 alexithymia test. Post hoc tests using Bonferroni test, indicated the following:

- Regarding the HADS, the mean score of the control group was significantly lower (Mean=8.50, SD=5.64) to the mean score of the CADASIL group (Mean=15.28; SD=7.49;p=.039) and the Sporadic CSVD group (Mean=17.17, SD=9.94; p=.005), with these clinical groups not differing between them (p = 1.00), indicating higher levels of depression and anxiety symptoms perceived in the CADASIL and Sporadic CSVD groups compared to controls.
- Regarding the HADS Anxiety sub score, the mean score for the control group (Mean=5.17, SD=3.50=) was significantly lower than for the Sporadic CSVD group (Mean=9.44., SD=5.54, p=.017), and only marginally lower to the CADASIL group (Mean=8.78; SD=4.05, p=.055). This suggests that, particularly the sporadic CSVD group has higher levels of anxiety comparatively to the healthy controls.
- Regarding the alexithymia score (TAS-20), post hoc tests revealed that the mean score for the control group (Mean= 29.94; SD=8.08), was significantly lower to both the CADASIL group (Mean=48.44, SD=7.39, p=.0001) and the sporadic CSVD group (Mean=51.17; SD=11.31, p=.0001), without differences between these two groups (p = 1.00). This suggests more difficulty in the CADASIL and Sporadic CSVD groups in identifying and dealing with emotions and emotional situations than healthy controls. (Table 3)

Table 1
Characteristics of the CADASIL group, the sporadic CSVD group and the matched healthy control group.

		CADASIL		Sporadic CSVD		Healthy Controls	
		N = 20		*N = 20*		*N = 20*	
		N/Mean	*%/ SD*	*N/ Mean*	*%/SD*	N/ Mean	%/ SD
Gender	Female	14	70 %	16	80 %	13	65 %
	Male	6	30 %	4	20 %	7	35 %
Age	Mean	56.06	*SD*=10.703	49.59	*SD*=10.038	*48.06*	*9.40*
	Min. – Max.	30 - 65		34 – 65		30–64	
Age group	30–40 years	4	20 %	4	20 %	5	25 %
	41–50 years	2	10 %	8	40 %	4	20 %
	51–60 years	6	30 %	3	15 %	7	32 %
	61–70 years	8	40 %	5	25 %	4	20 %
Formal Education	Primary (0–4 years)	5	25 %	4	20 %	1	5 %
	Basic (5–9 years)	4	20 %	3	15 %	5	25 %
	Secondary (10–12 years)	4	20 %	5	25 %	10	50 %
	Superior (more than 12 years)	7	35 %	8	40 %	4	20 %
Lacunar stroke (%)		4	20 %	2	10 %	0	0 %
WMH Lesion volume (cm3)		31.23	22.86	11.21	15.47	NA	
WMH Lesion load (Fazekas score 1–3)		2.75	0.62	1.88	0.69	NA	
Treated hypertension (%)		11	55 %	9	45 %	2	10 %
Diabetes (%)		3	15 %	2	10 %	0	0
Migraine (%)		8	40 %	11	55 %	0	0
Cognitive status (MoCA) *1–30*		22.50	5.11	22.22	4.62	24.74	3.24

Table 2
Group differences in cognitive assessment measures.

			Study group			
Cognitive assessment measures			CADASIL (*N* = 20)	Sporadic CSVD (*N* = 20)	Healthy controls (*N* = 20)	Sig. (p)
Digit Symbol Coding *(0–133)*		***M***	44.22	38.72	68.28	*Z* = 11.90
						.0001*
		SD	23.93	19.13	12.52	**Control > CADASIL = Sporadic CSVD**
FCSRT total immediate *(0–48)*		***M***	22.33	23.39	29.50	*Z* = 2.16
						.070
		SD	10.89	10.31	5.56	
FCSRT total delayed *(0–16)*		***M***	12.94	11.48	14.75	*Z* = 2.03
						.080
		SD	2.89	3.24	3.37	
FAB *(0–18)*		***M***	14.89	15.67	15.56	*Z* = 0.48
						.621
		SD	2.76	2.43	2.53	
Verbal Fluency	**Phonemic**	***M***	22.72	28.44	32.32	*Z* = 1.34
						.256
		SD	16.47	9.99	11.22	
	Semantic	***M***	32.33	26.50	35.56	*Z* = 4.08
						.023
		SD	11.97	9.25	7.08	
Month Ordering *(0–20)*		***M***	10.83	9.56	12.22	*Z* = 2.05
						.050
		SD	3.47	3.81	2.65	

* Group differences with Bonferroni correction *p*=.00625 (0.05/8). Data represents raw/unadjusted test scores.

3.2.2. Relationship between WMH lesion burden, socio-demographic characteristics, and neuropsychological performance

Despite of global cognitive and emotional similarities, lesion volume was found to be significantly different between the two clinical groups (CADASIL > Sporadic CSVD). Given that lesion load has found to be correlated with cognitive impairment in other studies [22,46], we tested the relationship between lesion burden and the neuropsychology status, taking the two clinical groups together as full sample. WMH volume was found to be correlated strongly and negatively with the digit-symbol coding (rho=−.453, *p*=.020). A linear regression showed that only 8 % of the variance of speed processing scores (Symbol-digit coding) are explained by lesion burden. No other correlations were found between lesion load and the remaining neuropsychological variables. When correlating WMH lesion burden with socio-demographic variables, we found a significant, strong, and positive correlation with age (rho=0.503; *p*=.009). Similarly, age significantly and positively correlates with speed processing performance (*r*=−.670; *p*=.003). No other correlations between lesion load, sociodemographic variables and neuropsychological test scores were found to be significant.

3.2.3. Neuropsychological profile in CADASIL and sporadic CSVD

To examine more in depth the profile of neuropsychological function of the groups, we transformed raw scores of the neuropsychological assessment instruments into z-scores using the procedure mentioned in the methods section.

In line with Fig. 1. global cognitive status is lower in CADASIL and Sporadic CSVD groups compared with controls, and there is an important slowing in speed processing in these groups compared with controls. Semantic fluency and working memory are particularly impoverished in the sporadic CSVD groups.

Regarding the socio-emotional profile (Fig. 2), impulsivity is higher in sporadic CSVD patients. Compared to controls, levels of apathy,

Table 3
Group differences in socio-emotional assessment measures.

Socio-emotional and behavioral assessment measures		Study group			
		CADASIL ($N = 20$)	Sporadic CSVD ($N = 20$)	Healthy controls ($N = 20$)	Sig. (p)
RTME (Theory of Mind) *0–32*	***M***	19.61	23.44	22.94	$Z = 1.63$ *.206*
	SD	9.56	5.74	4.41	
BIS–11 (Impulsivity) *30–120*	***M***	57.17	65.17	51.22	$Z = 4.37$ *.018*
	SD	11.57	5.81	5.46	
EA (Apathy) *0–30*	***M***	18.22	17.67	14.17	$Z = 4.30$ *.019*
	SD	5.04	4.67	3.68	
HADS (Depression and Anxiety total) *0–42*	***M***	15.28	17.17	8.50	$Z = 6.01$ ***.005****
	SD	7.49	9.94	5.64	
HADS Depression *0–21*	***M***	6.44	7.72	3.33	$Z = 4.82$ *.012*
	SD	3.95	5.31	2.49	
HADS Anxiety *0–21*	***M***	8.78	9.44	5.17	$Z = 5.49$ ***.007****
	SD	4.05	5.54	3.50	
TAS–20 (Alexithymia) *20–100*	***M***	48.44	51.17	29.94	$Z = 29.06$ *.0001**
	SD	7.39	11.31	8.08	

* Group differences with Bonferroni correction p=.00714 (0.05/7). Data represents raw/unadjusted test scores.

anxiety, depression, and alexithymia are clearly higher in both CADASIL and Sporadic CSVD groups, without a distinctive profile between the two clinical groups regarding these socio-emotional domains.

4. Discussion

The present study aimed to explore the characteristics of CADASIL and Sporadic CSVD patients in terms of cognitive, socio-emotional, and behavioral status, compared with a control group matched-for age, gender, and education. Despite unadjusted for other possible confounders, the comparison between the three groups, held to the conclusion that CSVD patients present slow speed processing compared to controls, despite a recent meta-analysis suggest cSVD-related cognitive impairments are more global than what was initial expected and to our findings. [47] Regarding the socio-emotional and behavioral status, both statistical tests and graphic analyses suggest that CADASIL and sporadic CSVD patients present significantly higher levels of depression and anxiety and exhibit higher traits of alexithymia compared to controls. Moreover, Sporadic CSVD patients revealed relatively higher levels of impulsivity than CADASIL participants. These emotional symptoms were not correlated with the lesion load, as it was found in previous studies (9, for a review), but this finding could have had the contribution of the sample size that was possibly underpowered to detect this. With a small sample size, all these findings should be considered as exploratory research. Nevertheless, the fact that a largely comprehensive battery of neuropsychological examination was deployed, and that the groups did not present cognitive impairment as measured by MOCA, underpin the relevance of these findings. Emotional deficits highlighted, namely alexithymia, anxiety, and depression, and in a lower extent apathy and impulsivity, account for deficits in emotion regulation and recognition in these patients of CSVD. Those findings may be, at least in part, explained by the white matter burden, that compromise cortical and subcortical networks that are responsible for emotion regulation. [19,20] However, given that this study is pivotal in a standardized assessment of several of these socio-emotional and behavioral domains, it would be extremely relevant to replicate a neuroimaging study analyzing these brain networks together with a rigorous and standardized assessment of the domains that have been shown affected in our patients. Even though symptoms like depression and apathy are already extensively described in cSVD literature regarding their neurophysiological substrates [16–18], more complex symptoms such as alexithymia, anxiety and impulsivity require further investigation. Anxiety was already explored in previous research

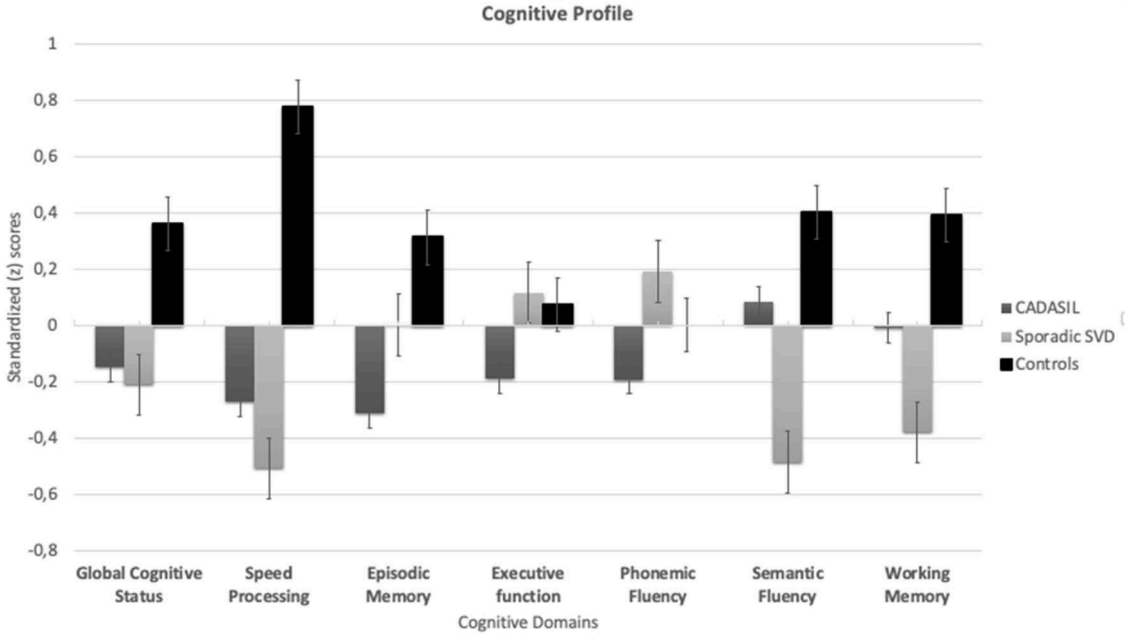

Fig. 1. Cognitive profile (z scores and standard errors) of test scores according to the group
Note: X-axis displays the cognitive domain and test, and the y-axis displays z-score values, the lines display composite scores for each group in each subdomain.

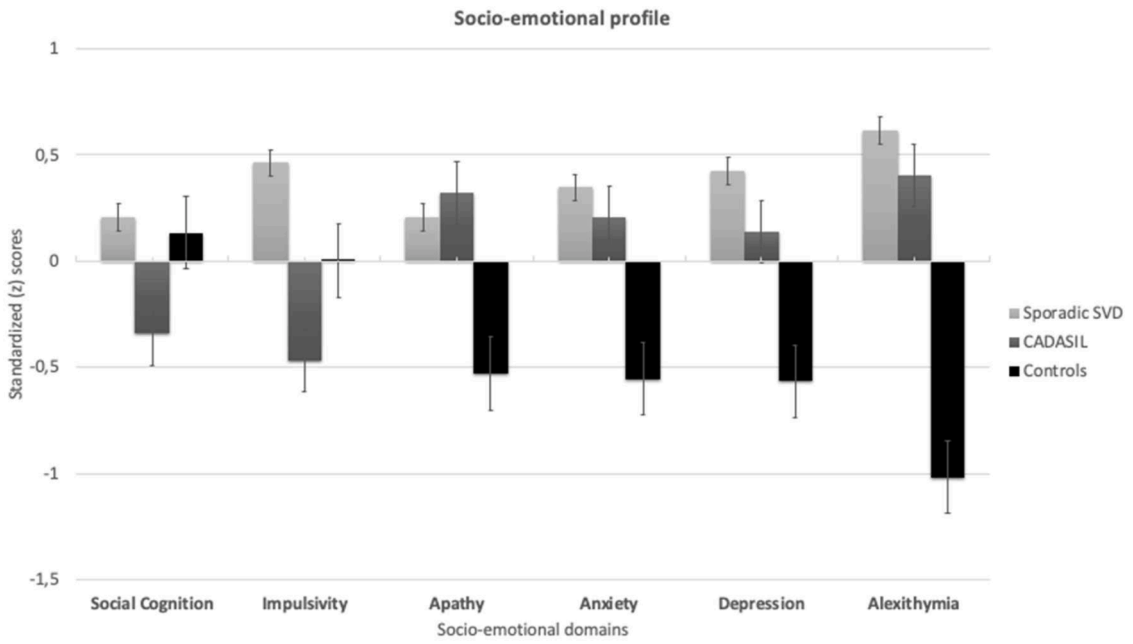

Fig. 2. Socio-emotional profile (z scores and standard errors) of test scores according to the group.
Note: X-axis displays the socio-emotional domain and test, and the y-axis displays z-score values, the lines display mean scores for each group in each subdomain.

with cSVD samples [48], but the measures used for anxiety symptoms were not adequate to exploit the relationship between cSVD neuroimaging data and anxiety further. Alexithymia, for example has not been examined before in cSVD patients, and a significant number of studies associates this trait to functional brain changes during emotional experiences, in areas such as medial prefrontal cortex, amygdala, and insula. [49] Additionally, despite social cognition has been studied in other cerebrovascular diseases (CVD) (e.g. multiple microinfarcts, hemorrhages, etc.,) [50,51], to our knowledge no study analyzed social cognitive performance in cSVD patients, and most studies with CVD patients relied only in collateral information from the available informants, which could be valuable data if correlated with self-report or performance based measures. With the inclusion of the Reading the Mind in the Eyes Test, [52] a widely used measure of the theory of mind, a domain of social cognition related with the ability to perceive and interpret emotions and thoughts from others, we highlight for the importance of this domain in future studies with this population. Given than affective symptoms appear to be highly prevalent in this population, studies point for a possible influence from the social cognition ability in the emotion perception and emotion recognition. [53] The current study does not allow to test for this relationship, but future studies should take these hypotheses in account.

These patients have significant non-cognitive symptoms, and this study suggests that these domains might be expressed in a prodromic stage of cSVD, when cognitive impairment is still not present, as elicited in recent findings [12]. This could be a valuable argument if we consider the fact that either the severity of the disease was not correlated with any of the socio-emotional variables, or any of the cognitive variables correlated with socio-emotional and behavioral domains. The cognitive changes that were present in our clinical samples (e.g. speed processing) were only associated with age and lesion burden, but to an higher extent with age, which is consistent with previous work [21,22]. A longitudinal approach to these patients would be extremely relevant to understand whether the emotional-behavioral symptoms are present throughout the disease lifespan and independently of the disease severity or aging.

This study has some important limitations, which accounts for its exploratory nature. The high number of measures and the lack of a sufficient sample to perform prediction and mediation analyses limits the generalizability of our findings. The small sample size required the use of the Bonferroni correction for differences between groups, which, according to the graphs depicting a clear non-overlap of confidence intervals for some symptoms like impulsivity, etc., suggests that this correction can be over-conservative. A power calculation would suggest an ideal total sample of around 160 patients. Nonetheless, CADASIL is a rare condition but extremely relevant as a pure model of cSVD, together with the efforts to match the three groups for age, gender, and education as extremely important variables for neuropsychological performance, held the current sample limitations. Concerning the clinical samples selection, the choice to select patients who undergone cerebral MRI in the last 12 months, despite allowing for higher accuracy and timely understanding with neuropsychological assessment moment, could have contributed to a selection bias. Relatively to the age matching, despite the mean age of the three groups does not differ statistically, the healthy control group had a small number of participants above 60 years old, given the lower availability of healthy volunteers with MRI scans, which is a limitation of the study, requiring a future study with a more representative sample. The differences between groups were also not adjusted for other possible confounders which accounts for possible limitations in its interpretation. The lack of normative data available for most of the instruments used also prohibited to take in consideration the demographics of the cognitive tests when obtaining z-score, which would considerably increase the fidelity of the findings. We additionally had some missing data in important measures (e.g. alexithymia), which requires a more cautious understanding of the findings. Our study also has some limitations concerning the neuroimaging data. First, the WMH was not corrected for total white matter volume or global intracranial volume. Second, while we choose to focus solely on white matter lesion burden, other neuroimaging variables, occurring in CSVD, can be implicated in the current findings, namely lacunar infarcts and cortical atrophy [54].

4.1. Conclusions

Despite the above limitations, our exploratory study may offer important contributions for research and clinical practice. The socio-emotional symptomatology present in cSVD should elicit an increase in the monitoring of these symptoms in the earlier stages of the disease, given that the current study identifies an impact both in younger and

older patients. The incorporation of new emotional and behavioral variables together in the assessment protocol is an important novelty and support a better understanding of the extent of deficits in emotion regulation behavior present in these patients. The fact that some clinical trials will probably come out in the next few years to test the efficacy of different approaches to treat CADASIL patients, highlights the relevance of a comprehensive protocol of neuropsychological assessment that includes socio-emotion evaluation. Despite of the existence of a neuropsychological protocol recommended for use in patients with vascular cognitive impairment [55], the protocol is mostly relying in cognitive measures, with exception to depression and global psychiatric symptoms, generally assessed by a relative or a health professional using the neuropsychiatric inventory. [27] Symptoms affecting emotion regulation and well-being [8] could be incorporated in clinical protocols for these patients since the beginning of clinical monitoring and as means to examine the clinical burden of the disease throughout the lifespan. Hopefully, this exploratory study will provide to future studies a more complete comprehensive protocol for better monitoring specific profiles of impairment in emotion and behavior function.

Data availability statement

The data that support the findings of this study are available from the corresponding author, ARS, upon reasonable request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors report there are no competing interests to declare.

Acknowledgments

We thank to the patients and relatives for their availability to participate in the study.

References

[1] A. Singh, G. Bonnell, J. De Prey, N. Buchwald, K. Eskander, K.J. Kincaid, et al., Small-vessel disease in the brain, Am. Heart J. Plus Cardiol. Res. Pract. 27 (2023), 100277. Mar 1.
[2] E.E. Smith, M. O'Donnell, G. Dagenais, S.A. Lear, A. Wielgosz, M. Sharma, et al., Early cerebral small vessel disease and brain volume, cognition, and gait, Ann. Neurol. 77 (2) (2015) 251–261. Feb.
[3] F. Han, F.F. Zhai, Q. Wang, L.X. Zhou, J. Ni, M. Yao, et al., Prevalence and risk factors of cerebral small vessel disease in a chinese population-based sample, J. Stroke 20 (2) (2018) 239–246. May.
[4] E.V. Backhouse, S.D. Shenkin, A.M. McIntosh, M.E. Bastin, H.C. Whalley, M. Valdez Hernandez, et al., Early life predictors of late life cerebral small vessel disease in four prospective cohort studies, Brain J. Neurol. 144 (12) (2021) 3769–3778. Dec 31.
[5] B.N. Huisa, G.A. Rosenberg, Binswanger's disease: toward a diagnosis agreement and therapeutic approach, Expert. Rev. Neurother. 14 (10) (2014) 1203–1213. Oct.
[6] E.J. van Dijk, N.D. Prins, H.A. Vrooman, A. Hofman, P.J. Koudstaal, M.M. B. Breteler, Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: rotterdam Scan study, Stroke 39 (10) (2008) 2712–2719. Oct.
[7] J.G. Baker, A.J. Williams, C.C. Ionita, P. Lee-Kwen, M. Ching, R.S. Miletich, Cerebral small vessel disease: cognition, mood, daily functioning, and imaging findings from a small pilot sample, Dement. Geriatr. Cogn. Disord. Extra 2 (1) (2012) 169–179. Jan.
[8] R.L. Brookes, T.A. Willis, B. Patel, R.G. Morris, H.S. Markus, Depressive symptoms as a predictor of quality of life in cerebral small vessel disease, acting independently of disability; a study in both sporadic small vessel disease and CADASIL, Int. J. Stroke 8 (7) (2013) 510–517.
[9] X. Xie, Y. Shi, J. Zhang, Structural network connectivity impairment and depressive symptoms in cerebral small vessel disease, J. Affect. Disord. 220 (2017) 8–14. Oct 1.
[10] Z. Fan, Y. Guo, X. Hou, R. Lv, S. Nie, S. Xu, et al., Selective impairment of processing task-irrelevant emotional faces in cerebral small vessel disease patients, Neuropsychiatr. Dis. Treat. 17 (2021) 3693–3703. Dec 16.
[11] R. Valenti, A. Poggesi, F. Pescini, D. Inzitari, L. Pantoni, Psychiatric disturbances in CADASIL: a brief review, Acta Neurol. Scand. 118 (5) (2008) 291–295. Nov.
[12] H. Chabriat, S. Lesnik Oberstein, Cognition, mood and behavior in CADASIL, Cereb. Circ. Cogn. Behav. 3 (2022), 100043.
[13] A.J. Thomas, R. Perry, R. Barber, R.N. Kalaria, J.T O'Brien, Pathologies and pathological mechanisms for white matter hyperintensities in depression, Ann. N. Y. Acad. Sci. 977 (2002) 333–339. Nov.
[14] L. Wouts, M. van Kessel, A.T.F. Beekman, R.M. Marijnissen, Oude Voshaar RC. empirical support for the vascular apathy hypothesis: a structured review, Int. J. Geriatr. Psychiatry 35 (1) (2020) 3–11. Jan.
[15] S.M. Noh, S.J. Chung, K.K. Kim, D.W. Kang, Y.M. Lim, S.U. Kwon, et al., Emotional disturbance in CADASIL: its impact on quality of life and caregiver burden, Cerebrovasc. Dis. 37 (3) (2014) 188–194. Basel Switz.
[16] C. Le Heron, S. Manohar, O. Plant, K. Muhammed, L. Griffanti, A. Nemeth, et al., Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease, Brain 141 (11) (2018) 3193–3210. Nov.
[17] O. Godin, C. Dufouil, P. Maillard, N. Delcroix, B. Mazoyer, F. Crivello, et al., White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study, Biol. Psychiatry 63 (7) (2008) 663–669. Apr 1.
[18] E. Jouvent, J.F. Mangin, E. Duchesnay, R. Porcher, M. Düring, Y. Mewald, et al., Longitudinal changes of cortical morphology in CADASIL, Neurobiol. Aging 33 (5) (2012) 1002.e29–1002.e36. May.
[19] A.M. Grool, Y. van der Graaf, W.P.T.M. Mali, T.D. Witkamp, K.L. Vincken, M. I. Geerlings, et al., Location and progression of cerebral small-vessel disease and atrophy, and depressive symptom profiles: the Second Manifestations of ARTerial disease (SMART)-Medea study, Psychol. Med. 42 (2) (2012) 359–370. Feb.
[20] M.J. Hollocks, A.J. Lawrence, R.L. Brookes, T.R. Barrick, R.G. Morris, M. Husain, et al., Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes, Brain J. Neurol. 138 (Pt 12) (2015) 3803–3815. Dec.
[21] J. Staals, T. Booth, Z. Morris, M.E. Bastin, A.J. Gow, J. Corley, et al., Total MRI load of cerebral small vessel disease and cognitive ability in older people, Neurobiol. Aging 36 (10) (2015) 2806–2811. Oct.
[22] Y. Shi, S. Li, W. Li, C. Zhang, L. Guo, Y. Pan, et al., MRI lesion load of cerebral small vessel disease and cognitive impairment in patients with CADASIL, Front. Neurol. [Internet] (2018) [cited 2023 Feb 2];9. Available from: https://www.frontiersin.org/articles/10.3389/fneur.2018.00862.
[23] C.N. Kan, B. Gyanwali, S. Hilal, K.P. Ng, N. Venketasubramanian, C.L.H. Chen, et al., Neuropsychiatric correlates of small vessel disease progression in incident cognitive decline: independent and interactive effects, J. Alzheimers. Dis. JAD 73 (3) (2020) 1053–1062.
[24] J. Hogeveen, J. Grafman, Alexithymia, Handb. Clin. Neurol. 183 (2021) 47–62.
[25] K.J. Noh, S. Chung, J. Lim, G. Kim, H. Jeong, Speech emotion recognition framework based on user self-referential speech features, in: Proceedings of the IEEE 7th Global Conference on Consumer Electronics, GCCE 2018, Nara, Japan, IEEE, 2018, pp. 341–342. October 9-12, 2018.
[26] J.G. Harris, C.M. Filley, CADASIL: neuropsychological findings in three generations of an affected family, J. Int. Neuropsychol. Soc. JINS 7 (6) (2001) 768–774. Sep.
[27] U. Clancy, D. Gilmartin, A.C.C. Jochems, L. Knox, F.N. Doubal, J.M. Wardlaw, Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis, Lancet Psychiatry 8 (3) (2021) 225–236. Mar 1.
[28] A. Olsson, K.N. Ochsner, The role of social cognition in emotion, Trends Cogn. Sci. 12 (2) (2008) 65–71. Feb.
[29] Y. Suchy, J.A Holdnack, J.A. Holdnack, L.W. Drozdick, L.G. Weiss, G.L. Iverson, Chapter 8 - assessing social cognition using the ACS for WAIS–IV and WMS–IV. WAIS-IV, WMS-IV, and ACS [Internet], Academic Press, San Diego, 2013, pp. 367–406 [cited 2023 Jun 29]Available from, https://www.sciencedirect.com/science/article/pii/B9780123869340000080.
[30] H. Chabriat, A. Joutel, M. Dichgans, E. Tournier-Lasserve, M.G. Bousser, Cadasil, Lancet Neurol. 8 (7) (2009) 643–653. Jul.
[31] M.R. Almeida, I. Elias, C. Fernandes, R. Machado, O. Galego, G. Santo, NOTCH3 mutations in a cohort of portuguese patients within CADASIL spectrum phenotype, Neurogenetics 23 (1) (2022) 1–9. Jan 1.
[32] S. Freitas, M.R. Simões, L. Alves, I. Santana, Montreal cognitive assessment: influence of sociodemographic and health variables, Arch. Clin. Neuropsychol. 27 (2) (2012) 165–175. Mar 1.
[33] L. Pantoni, Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges, Lancet Neurol. 9 (7) (2010) 689–701. Jul.
[34] S. Freitas, M.R. Simões, L. Alves, I. Santana, Montreal cognitive assessment (MoCA): normative study for the Portuguese population, J. Clin. Exp. Neuropsychol. 33 (9) (2011) 989–996. Nov.
[35] WAIS-III - Escala De Inteligência de Wechsler para Adultos - 3a Edição – Hogrefe Editora [Internet], WAIS-III. [cited 2023 Jul 1]. Available from: https://www.hogrefe.com/pt/shop/escala-de-inteligencia-de-wechsler-para-adultos-3-edic-o.html.
[36] I. Buekenhout, J. Leitão, A.A. Gomes, A new test for the assessment of working memory in clinical settings: validation and norming of a month ordering task, Psychol. Assess. 30 (10) (2018) 1367–1381. Oct.
[37] C.F. Lima, L.P. Meireles, R. Fonseca, S.L. Castro, C. Garrett, The frontal assessment battery (FAB) in Parkinson's disease and correlations with formal measures of executive functioning, J. Neurol. 255 (11) (2008) 1756–1761. Nov.

[38] S. Cavaco, A. Gonçalves, C. Pinto, E. Almeida, F. Gomes, I. Moreira, et al., Semantic fluency and phonemic fluency: regression-based norms for the portuguese population, Arch. Clin. Neuropsychol. 28 (3) (2013) 262–271. May.
[39] R. Lemos, A. Afonso, C. Martins, J.H. Waters, F.S. Blanco, M.R. Simões, et al., Selective reminding and free and cued selective reminding in mild cognitive impairment and alzheimer disease, Appl. Neuropsychol. Adult. 23 (2) (2016) 85–93.
[40] J. Pestana, M.S.S.P.C. Menéres, M.J.P.M. Gouveia, R.F. Oliveira, The reading the mind in the eyes Test: a Portuguese version of the adults' test, Análise. Psicológica. 36 (3) (2018) 369–381.
[41] P. Pechorro, J. Maroco, J.V. Ray, R.A. Gonçalves, Psychometric properties of the barratt impulsiveness Scale version 11 among a Portuguese sample of incarcerated juvenile offenders, Psychol. Crime Law 21 (9) (2015) 854–870. Oct 21.
[42] The portuguese version of the 20-item Toronto alexithymia scale – I. linguistic adaptation, semantic validation, and reliability study, |, Acta Méd. Port. [Internet] (2023) [citedJul 1]. Available from, https://actamedicaportuguesa.com/revista/index.php/amp/article/view/1884/0.
[43] L. Caeiro, T. Silva, J.M. Ferro, J.L.P. Ribeiro, M.L. Figueira, Metric properties of the Portuguese version of the apathy evaluation scale, Psicol. Saúde. Doenças. 13 (2012) 266–282.
[44] J. Pais-Ribeiro, I. Silva, T. Ferreira, A. Martins, R. Meneses, M. Baltar, Validation study of a Portuguese version of the hospital anxiety and depression scale, Psychol. Health Med. 12 (2) (2007) 225–235. Marquiz 235–7.
[45] F. Fazekas, J.B. Chawluk, A. Alavi, H.I. Hurtig, R.A. Zimmerman, MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (2) (1987) 351–356. Aug.
[46] B. Patel, H.S. Markus, Magnetic resonance imaging in cerebral small vessel disease and its use as a surrogate disease marker, Int. J. Stroke 6 (1) (2011) 47–59. Off J. Int. Stroke Soc.Feb.
[47] O.K.L. Hamilton, E.V. Backhouse, E. Janssen, A.C.C. Jochems, C. Maher, T. E. Ritakari, et al., Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis, Alzheimers. Dement J. Alzheimers Assoc. 17 (4) (2021) 665–685. Apr.
[48] L.L. Shan, Y.L. Wang, T.C. Qiao, Y.F. Bian, Y.J. Huo, C. Guo, et al., Association of serum interleukin-8 and serum amyloid a with anxiety symptoms in patients with cerebral small vessel disease, Front. Neurol. 13 (2022) [Internet][cited 2023 Jun 30]Available from: https://www.frontiersin.org/articles/10.3389/fneur.2022.938655.
[49] J. van der Velde, M.N. Servaas, K.S. Goerlich, R. Bruggeman, P. Horton, S. G. Costafreda, et al., Neural correlates of alexithymia: a meta-analysis of emotion processing studies, Neurosci. Biobehav. Rev. 37 (8) (2013) 1774–1785. Sep.
[50] S. Zhu, X. Cheng, M. Ai, X. Liu, Social cognitive impairment in patients with stroke, Int. J. Cerebrovasc. Dis. (2020) 701–708.
[51] P. Njomboro, Social cognition deficits: current position and future directions for neuropsychological interventions in cerebrovascular disease, Behav. Neurol. 2017 (2017), 2627487.
[52] S. Baron-Cohen, S. Wheelwright, J. Hill, Y. Raste, I. Plumb, The 'reading the mind in the eyes' test revised version: a study with normal adults, and adults with asperger syndrome or high-functioning autism, J. Child Psychol. Psychiatry 42 (2) (2001) 241–251. Feb.
[53] P.J. Eslinger, K. Parkinson, S.G. Shamay, Empathy and social-emotional factors in recovery from stroke, Curr. Opin. Neurol. 15 (1) (2002) 91–97. Feb.
[54] F. De Guio, M. Duering, F. Fazekas, F.E. De Leeuw, S.M. Greenberg, L. Pantoni, et al., Brain atrophy in cerebral small vessel diseases: extent, consequences, technical limitations and perspectives: the HARNESS initiative, J. Cereb. Blood Flow Metab. 40 (2) (2020) 231–245. Feb.
[55] V. Hachinski, C. Iadecola, R.C. Petersen, M.M. Breteler, D.L. Nyenhuis, S.E. Black, et al., National institute of neurological disorders and stroke–canadian stroke network vascular cognitive impairment harmonization standards, Stroke 37 (9) (2006) 2220–2241. Sep.