



HAL
open science

CADA-PRO, a patient questionnaire measuring key cognitive, motor, emotional and behavioral Outcomes in CADASIL

Cécile Di Folco, Aude Jabouley, Sonia Reyes, Carla Machado, Stéphanie Guey, Dominique Hervé, Fanny Fernandes, Joseph Agossa, Hugues Chabriat, Sophie Tezenas Du Montcel

► **To cite this version:**

Cécile Di Folco, Aude Jabouley, Sonia Reyes, Carla Machado, Stéphanie Guey, et al.. CADA-PRO, a patient questionnaire measuring key cognitive, motor, emotional and behavioral Outcomes in CADASIL. Stroke, 2024, Online ahead of print. 10.1161/STROKEAHA.124.047692 . hal-04689163

HAL Id: hal-04689163

<https://hal.science/hal-04689163v1>

Submitted on 5 Sep 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 CADA-PRO, a patient questionnaire measuring key cognitive, motor, emotional
2 and behavioral Outcomes in CADASIL

3 Cécile Di Folco¹, MS, Aude Jabouley², MS, Sonia Reyes², MS, Carla Machado², MS, Stéphanie Guey^{2,3},
4 MD, PhD, Dominique Hervé^{2,3}, MD, Fanny Fernandes², PhD, Joseph Agossa¹, MS, Hugues Chabriat^{2,3*}
5 MD, PhD, and Sophie Tezenas du Montcel^{1*}, MD, PhD

6 *HC and STM are equivalent last authors

7
8 Affiliations:

9 ¹ARAMIS, Sorbonne Université, Institut du Cerveau-Paris Brain Institute-ICM, CNRS, Inria, Inserm, AP-HP,
10 Groupe Hospitalier Sorbonne Université, Paris, France

11 ²Centre de Référence pour les maladies vasculaires rares du cerveau et de l'œil (CERVCO) and Centre
12 Neurovascular Translationnel (CNVT)

13 ³INSERM U1141 – FHU NeuroVasc, Université Paris Cité

14
15 Corresponding author: Sophie Tezenas du Montcel, Département d'information médicale (DIM) - GHU
16 APHP Sorbonne Université site Pitié Salpêtrière, 47-83 boulevard de l'Hôpital, 75651 Paris cedex 13,
17 France. Tel.: +33 0 142160582; E-mail: sophie.tezenas@aphp.fr.

18
19 Keywords

20 instrument development; reliability; validity; CADASIL; cSVD; PROM

21
22 Total word count

23 6,035

24
25
26 Cover Title: CADA-PRO, a patient questionnaire for CADASIL

27
28 Tables 2; Figures 3

29

30 **Non-standard Abbreviations and Acronyms**

31

32 CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy;

33 cSVD = cerebral Small Vessel Disease;

34 EF = Executive Functions;

35 EFA = Exploratory Factor Analysis.

36 FCSRT = Free and Cued Selective Reminding Test;

37 HAD = Hospital Anxiety and Depression scale;

38 PGIC = Patient Global Impression of Change;

39 SAS = Starkstein Apathy Scale;

40 SSPB-4 = Short Physical Performance Battery (4 items);

41 TMT = Trail Making Test;

42 VADAS-Cog = Vascular Dementia Assessment Scale cognitive subscale;

43 SDMT = Symbol-Digit Modalities Test;

44 WCST = Wisconsin Card Sorting Test;

45 WMS-III = Weschler Memory Scale 3rd revision;

46

ABSTRACT

Background

Cerebral Small Vessel Disease (cSVD) of ischemic type, either sporadic or genetic, as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), can impact the quality of daily life on various cognitive, motor, emotional or behavioral aspects. No instrument has been developed to measure these outcomes from the patient's perspective. We thus aimed to develop and validate a patient-reported questionnaire.

Methods

In a development study, 79 items were generated by consensus between patients, family representatives and cSVD experts. A first sample of patients allowed assessing the feasibility (missing data, floor and ceiling effect, acceptability), internal consistency, and dimensionality of a first set of items. Thereafter, in a validation study, we tested a reduced version of the item set in a larger sample to assess the feasibility, internal consistency, dimensionality, test-retest reliability, concurrent validity, and sensitivity to change.

Results

The scale was developed in 44 cSVD patients and validated in a second sample of 89 individuals (including 43 patients with CADASIL and 46 with another cSVD). The final CADASIL Patient-Reported Outcome (CADA-PRO) scale comprised 18 items covering four categories of consequences (depression/anxiety, attention/executive functions, motor, daily activities) of the disease. The proportion of missing data was low, no item displayed major floor or ceiling effect. Both the internal consistency and test-retest reliability were good (Cronbach alpha=0.95, intraclass correlation coefficient=0.88). In patients with CADASIL, CADA-PRO scores correlated with the modified Rankin scale, Starkstein Apathy Scale (SAS), Hospital Anxiety and Depression scale (HAD), Working Memory Index, and Trail Making Test times. In patients with other cSVDs, CADA-PRO correlated only with HAD and SAS.

Conclusion

The CADA-PRO may be an innovative instrument for measuring patient-reported outcomes in future cSVD trials. Full validation was obtained for its use in CADASIL patients, but further improvement is needed for its application in other cSVDs.

INTRODUCTION

Cerebral small vessel disease (cSVD) is a leading cause of stroke, cognitive decline and disability.¹ Alongside sporadic forms of cSVD, whose prevalence in the general population is considerable¹, various genetic cSVDs have been identified since the 1990s.² Among these, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is, by far, the most frequently diagnosed hereditary cSVD worldwide.³ The disease recapitulates most manifestations observed in multiple sporadic or genetic forms of cSVD. In preclinical CADASIL mouse models, key disease mechanisms have recently been deciphered.⁴ Various therapeutic approaches can now be envisaged to obtain disease-modifying treatments in the next future.

In clinical terms, however, a number of obstacles still need to be overcome to assess future therapies in CADASIL. Although the condition is considered as an archetypal cSVD, CADASIL remains a rare disorder.⁵ It evolves variably and over multiple decades. The clinical spectrum is broad.^{3,6} These difficulties are further complicated by the varying degrees of symptom awareness felt by the patients themselves, apprehension depending on the family's experience of the disease, or support by relatives or socio-medical resources. Hence, not only the right treatment should be tested for the right person at the right time, but it will be just as crucial to show in a robust manner that the treatment addresses clinically relevant issues that are actually meaningful to the patients.⁷ Patient Reported Outcomes Measures (PROM) are increasingly developed exactly for this purpose and become recommended to support claims in approved medical product by regulatory agencies.^{8,9}

97 In the present study, we aimed to assess the first self-reported questionnaire developed to capture
98 different patient reported outcomes in cSVD. The tool that we called CADA-PRO was developed in
99 collaboration with CADASIL patients, family representatives, psychologists, and clinicians to cover
100 multidimensional consequences of the disease on daily living at early or intermediate stage of the disease.
101 The tool properties were investigated according to the COnsensus-based Standards for the selection of
102 health status Measurement INstruments (COSMIN) guideline.¹⁰

103
104

105 **METHODS**

106

107 **DATA AVAILABILITY**

108 Anonymized data not published within this article will be made available upon request from any
109 qualified investigator.

110

111 **GENERAL STUDY PLAN**

112

113 The feasibility and validity of the CADA-PRO scale were assessed using a two-stage procedure
114 comprising a development study and a validation study. Two distinct samples of patients were used for
115 these two studies.

116 In the development study, multiple questions or items were first generated by experts, patients and
117 family members. Thereafter, a first sample of patients diagnosed with CADASIL or other cSVD was
118 recruited to assess the feasibility, internal consistency, and dimensionality of this first set of items. Patients'
119 caregivers were also recruited to evaluate a caregiver version of the set of items.

120 In the validation study, a reduced set of items was chosen and assessed in a larger sample of
121 patients for the feasibility, internal consistency, reliability, dimensionality, concurrent validity, and sensitivity
122 to change.

123 The psychometric properties of the final set of items were finally analyzed.

124

125 **THE CADA-PRO DEVELOPMENT STUDY**

126

127 **Participants**

128

129 Patients participating to the development study were enrolled from January 2020 to May 2021 at
130 the French Referral Centre for rare cerebrovascular diseases (CERVCO). They were recruited at day
131 hospital or during outpatient consultations planned for work-up after a recent stroke event or an MRI-based
132 diagnosis of ischemic cSVD. The recruitment target was fixed at 50 patients. Additional inclusion criteria
133 were: 1) Age>18 years, 2) French native speaking and literacy, 3) Independent ability to complete
134 questionnaires, 4) confirmed diagnosis of a typical ischemic cSVD (white matter hyperintensities with or
135 without lacunes or microbleeds) at MRI examination. Exclusion criteria were non-acquired cognitive
136 disability, nonvascular leukoencephalopathy, suspicion of degenerative disease, severe or unstabilized
137 psychiatric pathologies, and unstable clinical state (seizures or recent stroke).

138 To evaluate the patient caregiver's questionnaire, individuals were selected if they were easily
139 reachable, informative and in contact with the patient at least once every 15 days.

140

141 **Setting up the initial questionnaire**

142

143 All items of the questionnaire were first developed together by 1) four psychologists with extensive
144 experience in assessing patient complaints, listening to difficulties of patients, caregivers, and families and
145 evaluating cognitive performances and neuropsychiatric disturbances (CM, AJ, MHD, SR), 2) four patients
146 (or their representatives) belonging to the CADASIL French Family Association (CADASIL-France), 3) two
147 neurologists (HC, DH) having a long experience in patient care and follow-up. These items were chosen to
148 evaluate cognitive, emotional, behavioral, and motor symptoms potentially impacting daily living. After in-
149 depth discussion during repeated meetings involving all (n=2) or some members of these groups (n=4), 79
150 Likert-scaled items were selected and sorted (Table S1).

151

152 **Questionnaire administration and evaluation**

153

154 During the questionnaire administration performed at hospital, study participants were asked
155 whether the questionnaire items were understandable, accurately and exhaustively represented their

156 everyday difficulties with the disease, could be answered without assistance, and were emotionally difficult
157 to answer. Individuals were also asked to give out cognitive, motor, emotional, behavioral, and everyday
158 difficulties that would be missing from these first questions.

159 Data Analysis

161 We first analyzed the characteristics of patients included in the study, the frequency of missing
162 data, and floor and ceiling effects on each item. The internal consistency of the questionnaire was
163 evaluated using Cronbach's alpha and its structure was assessed using an Exploratory Factor Analysis
164 (EFA). Prior to EFA, missing data were imputed with Multivariate Imputation by Chained Equations (MICE)
165 algorithm.

167 **THE CADA-PRO VALIDATION STUDY**

169 Participants

171 Patients participating to the validation study were enrolled from November 2021 to February 2023.
172 They were recruited and selected according to the same procedures as those used in the development
173 study. The initial recruitment target was 100 patients.

174 Setting up the validation questionnaire

175 The validation questionnaire was prepared based on the results of the development study. Each
176 item of the first questionnaire was kept for the validation study when it fulfilled the following criteria: 1) less
177 than 20% of missing data, 2) less than 60% of answers at floor or ceiling modality, 3) did not decrease the
178 Cronbach's alpha of the set of items, 4) highest loading among items measuring the same trait.

180 Questionnaire administration and evaluation

181 All participants completed the CADA-PRO questionnaire at hospital on the day of inclusion in the
182 validation study, one month later when they were alone at home (M1), and one year later during a follow-up
183 visit at hospital (M12).

184 To establish the external validity of the final questionnaire, an extensive clinical evaluation was
185 performed at the day of inclusion and during the one-year follow-up visit at hospital. This included a large
186 battery of cognitive tests and a global assessment of disability, motor disturbances, mood, and behavior.
187 Order between the CADA-PRO completion and neuropsychological assessments was randomized.

188 Mental flexibility and processing speed were evaluated using seven scores. One was the number
189 of correct answers at the Vascular Dementia Assessment Scale cognitive subscale (VADAS-Cog) Symbol
190 Digit Modalities Test (SDMT).¹¹⁻¹³ Four were obtained from the Trail Making Test (TMT): the time for
191 completion of TMT part A (TMT A time) and TMT part B (TMT B time), their difference (TMT B-A time), and
192 the Number of Errors in TMT part B.^{14,15} Two were obtained from the Wisconsin Card Sorting Test
193 (WCST)¹⁶: the number of completed categories and the number of perseverations. Working memory was
194 assessed using the Working Memory Index from the Weschler Memory Scale 3rd revision (WMS-III).¹⁷
195 Verbal memory performance was analyzed using scores obtained from the Free and Cued Selective
196 Reminding Test (FCSRT) adapted from the Grober and Buschke procedure¹⁸: the total Free Recall and
197 total Cued Recall scores, as well as the Index of Sensitivity to Cueing, a measure of retrieval/storage
198 ability.¹⁹

199 Motor symptoms were evaluated using 4 items from the Short Physical Performance Battery
200 (SSPB)²⁰: Standing Balance Test with 1) side by side feet, 2) feet in Tandem, 3) single foot stand, and
201 Single Chair Stand Test. A SSPB-4 score was computed as the sum of these four items.
202
203
204
205
206

207 Emotional and behavioral symptoms were evaluated with the Hospital Anxiety and Depression
208 scale (HAD)²¹, and the Starkstein Apathy Scale (SAS).²²

209 Disability was assessed using the modified Rankin scale. Daily living activities and functional
210 independence were evaluated globally using the Instrumental Activities of Daily Living (IADL) scale.²³

211
212 At the final visit, patients were further asked to complete the Patient Global Impression of Change
213 (PGIC).²⁴

214 215 Data analysis

216
217 We first analyzed the main characteristics of all participants in the validation study at inclusion, M1
218 and M12. We also compared these characteristics between patients with CADASIL and patients with other
219 types of cSVD.

220 As for the development study, we checked the frequency of missing data, floor and ceiling effects
221 on each item. More specifically, the different items were kept if they: 1) had less than 20% of missing data,
222 2) had less than 60% of answers at floor or ceiling modality, 3) did not decrease the Cronbach's alpha of
223 the set of items.

224 To analyze the properties and structure of the validation questionnaire, we used a Confirmatory
225 Multidimensional Item Response Theory Model. Items with insufficient communalities (<0.4) were removed.
226 The item selection process is summarized in Figure S1.

227 Then, we computed the total CADA-PRO score as the unweighted sum of all questionnaire items.
228 In addition, for each factor estimated in the structure analysis, we calculated a sub-score as the unweighted
229 sum of the corresponding items. The total score was not computed for patients having more than 20% of
230 missing data. For patients with less than 20% missing data, if only one value was missing per sub-score, it
231 was imputed using the average of the items belonging to the same sub-score. Patients for whom the
232 CADA-PRO total score could not be computed were excluded from the analysis. The effect of order
233 between the CADA-PRO completion and neuropsychological assessments on the CADA-PRO total score
234 was checked.

235 We also assessed the test-retest reliability between the results obtained at inclusion and at one-
236 month completion using quadratic-weighted Cohen's Kappas at each item level and the Intraclass
237 Correlation Coefficient (ICC) at the score and sub-score levels. For scores and sub-scores, we further
238 calculated the Standard Error of Measurement (SEM) and Smallest Detectable Change (SDC) between
239 measures obtained at inclusion and one-month completion. SEM was computed as $SD \times \sqrt{1-ICC}$, where
240 SD was the standard deviation of all measures of the considered CADA-PRO score. SDC was then
241 computed as $SEM \times 1.96 \times \sqrt{2} / \sqrt{n}$, where n was the number of all measures of the same CADA-PRO score.

242 We further conducted concurrent validity analysis separately for each diagnosis group (CADASIL
243 or other cSVD). First, we computed the correlations between CADA-PRO scores and clinical scores that
244 had enough variability within our sample (SAS, HAD anxiety and depression, VADAS-Cog code, Working
245 Memory Index from WMS-III, SSPB-4, FCSRT total free recall and reactivity index, TMT B-A). Second, we
246 performed a multiple regression to explain the CADA-PRO total score by the clinical scores selected
247 through a stepwise variable selection.

248 Finally, we assessed sensitivity to change between inclusion and 1-year completion. We computed
249 the mean score difference between the two assessments, the p-value of a two-tailed T-test testing if this
250 mean score difference was different from 0, as well as the corresponding effect size (mean score difference
251 divided by the standard deviation of score difference).

252
253 For two-group comparisons, T-tests were performed on quantitative variables, Mann-Whitney U test on
254 modified Rankin Score, and Chi-square tests on categorical variables. For more than two-group
255 comparisons in quantitative values, ANOVA were performed, and for significant differences, Tukey-Kramer
256 adjusted pairwise comparisons were performed. Data were expressed as mean \pm standard deviation or
257 frequency (percent). Statistical tests were performed at the conventional 2-tailed type I error of 0.05. Data

258 were analyzed using R version 4.0.3 (The R Foundation for Statistical Computing, 2020) and Python 3.8.
259 The reporting of the results of the validation study is in accordance with the STROBE (Strengthening the
260 Reporting of Observational Studies in Epidemiology) reporting guideline.²⁵

261

262 **STANDARD PROTOCOL APPROVAL, REGISTRATION, AND PATIENT CONSENTS**

263 Informed consent was obtained from each subject or from a close relative if necessary. Data were
264 collected through the SMACS study, that was approved by an independent ethics committee (2019-
265 A01892-55).

266

267 **RESULTS**

268

269 **THE CADA-PRO DEVELOPMENT STUDY**

270

271 Forty-four individuals participated to the CADA-PRO development study using the initial version of
272 the CADA-PRO questionnaire. One patient was diagnosed with CADASIL, 7 had a monogenic cSVD
273 distinct from CADASIL (mutation of COL4A1/COL4A2) and 36 displayed a sporadic form of cSVD related to
274 aging, hypertension or other vascular risk factors (Table 1, see Table S1 for more details).

275

276 Out of the 79 items initially selected for the CADA-PRO questionnaire (Table S2), 11 were
277 excluded due to too many missing data: these items concerned driving and professional activities, which
278 are not relevant for all patients (Figure S2). 26 items were further excluded due to the presence of an
279 obvious floor or ceiling effect (Figure S2). These items mostly assessed severe limitations that are not
280 encountered in the early stage of the disease (for example: need help in daily activities, severe depressive
281 or reduced mobility). Two items were further excluded because they were found to decrease Cronbach's
282 alpha of the total set of questions. Finally, 20 additional items were excluded due to their insufficient weight
283 in the four first dimensions estimated by the EFA and corresponding to 1) the difficulties in activities of daily
284 living, 2) the changes in attention and executive functions (EF), 3) the development of motor symptoms,
285 and 4) the occurrence of anxiety and depression (Table S3). One item corresponding to a frequent
286 complaint was also added to the final version based on experts' recommendations (Figure S1).

287 As only 70% of patients had a caregiver, and after we observed that caregiver answers were too
288 discordant with those obtained from the patients (Figure S3), the caregiver version of the CADA-PRO
289 questionnaire was not further developed.

290

291 **THE CADA-PRO VALIDATION STUDY**

292

293 Ninety-two patients participated to the CADA-PRO validation study, of whom 89 answered the
294 questionnaire with at least 80% of complete data. Of them, 43 were diagnosed with CADASIL, six had a
295 monogenic cSVD distinct from CADASIL (mutation of COL4A1/COL4A2, N=3; mutation of HTRA1, N=3)
296 and 40 presented with a sporadic form of cSVD related to aging, hypertension or other vascular risk
297 factors. Patients with a cSVD distinct from CADASIL were older at inclusion (56.7 ± 11.8 vs. 64.0 ± 13.1 ,
298 $p=0.007$) and at time of diagnosis (49.5 ± 11.7 vs. 59.0 ± 11.9 , $p<0.001$) than CADASIL patients. They also
299 had worse performances for the VADAS-Cog SDMT and Index of sensitivity to cueing from the FCSRT
300 (Table S4).

301

302 Feasibility

303 The administered CADA-PRO questionnaire included 20 items selected from the development
304 study. None of them displayed excessive missing data, floor or ceiling effect (Figure 1). The average
305 proportion of missing data was 1.3% (SD=1.6%, max=6.7% reached on item 10 i.e. Lose self-esteem). The
306 average proportion of answers on the floor modality was 24.1% (SD=10.4%, max=50.0% reached on item

307 7 i.e. Give up most daily activities) and that of the ceiling modality was 12.7% (SD=6.9%, max=30%
308 reached on Item 18 i.e. Walk less).

309
310 Structure

311 We applied the four-factor structure derived from the development study to the data collected in the
312 validation study. For this purpose, each item was constrained to load on only one latent factor (Table S3).
313 Two items (1–Difficulty following conversation and 2–Write everything down not to forget) were found to be
314 insufficiently explained by the model (communalities<0.4). They were removed.

315 The final structure (Figure 2) based on 18 items along 4 main dimensions included: 1) 5 items
316 assessing the impact of the disease on daily activities (“Daily activities”), 2) 6 items related to anxiety and
317 depressive complaints (“Anx/Dep”), 3) 4 items related to impairment in attention and executive functions
318 (“Attention/EF”), and 4) 3 items covering the motor difficulties (“Motor”). These four factors respectively
319 explained 15.2%, 26.7%, 17.7%, and 15.8% of the variance (RMSEA=0.17 (0.15;0.19), TLI=0.89,
320 CFI=0.91).

321 The CADA-PRO total score computed as the sum of the 18 different items, ranged from 0 – no
322 complaint to 72 – maximum complaint. The average score was 30.0 (SD=17.2) for patients with CADASIL,
323 and 30.3 (SD=16.3) for patients with other types of cSVDs. The total score did not depend on completion
324 order (neuropsychological testing/questionnaire; data not shown). The final CADA-PRO items in French are
325 available in Table S5.

326
327 Internal consistency

328 The Cronbach’s alpha of final CADA-PRO was 0.95 (0.92;0.97) (Table 2). No removal of item was
329 increasing the Cronbach’s alpha (Table S6). The Cronbach’s alpha for the different sub-scores ranged from
330 0.91 (0.87;0.95) (Depression/Anxiety) to 0.84 (0.75;0.90) (Attention/EF).

331
332 Test-retest reliability

333 The reliability of the total score was high with an ICC between the score obtained at inclusion and
334 at M1 of 0.88 (0.80;0.92) (p value=3.5e-22). ICC was above 0.8 for all sub-scores except the Attention/EF
335 one. Fourteen items displayed substantial reliability (κ >0.6), three showed moderate reliability
336 (κ >0.5), and one showed low reliability (κ <0.4) (Table 3). At the group level, the smallest
337 detectable change in the total score was 2.06 points (range: 1.66-2.62).

338
339 Concurrent validity

340 The CADA-PRO total score was significantly related to the Rankin score for patients with CADASIL
341 but not for the others (Anova $F=7.03$, p -value<0.001; see Figure 3 A and B). For CADASIL patients, the
342 CADA-PRO score significantly correlated with the SAS, HAD-depression, and HAD-anxiety scores, Rankin
343 Score, Working Memory Index and with TMT B-A time (Figure 3 C). Correlations between the CADA-PRO
344 score and other clinical scores were all higher for CADASIL patients than for patients with other cSVDs ,
345 except for HAD-anxiety (Figure 3 D). For patients with other cSVDs, the CADA-PRO score significantly
346 correlated only with the SAS, HAD-depression, and HAD-anxiety scores.

347 At the level of the four-domain sub-scores, for patients with CADASIL, the correlations showed
348 different patterns: the Anxiety-Depression score had the highest correlation with HAD anxiety ($r=0.70$,
349 $p<0.001$), depression ($r=0.78$, $p<0.001$) and the SAS scores ($r=0.61$, $p<0.001$), but does not correlate with
350 other scores. In comparison, the Motor score has the highest correlation with the Rankin score ($r=0.65$,
351 $p<0.001$), and tends to correlate with most clinical scores, significantly for TMT A and B-A times ($r=0.38$,
352 $p=0.010$, and $r=0.47$, $p=0.0015$, resp.). Attention/EF and Impact on daily activities scores have a correlation
353 pattern similar to that of the Motor score.

354 To further understand the association between the CADA-PRO total score and the clinical status,
355 we regressed the total score on the different clinical scores using a stepwise selection procedure (Table S7
356 and Figure S4). For patients with CADASIL, we found a significant effect of HAD anxiety ($\beta=4.7$ (2.1;7.4),
357 $p=0.001$), HAD depression ($\beta=9.6$ (6.9;12.3), $p<0.001$), and Working Memory Index ($\beta=-2.3$ (-4.6;-0.09),

358 p=0.042), accounting for 66.7% of the CADA-PRO score variance. For patients with other cSVDs, only
359 HAD anxiety ($\beta=4.3$ (1.7;6.9), $p=0.001$) and HAD depression ($\beta=10.5$ (7.8;13.1), $p<0.001$) significantly
360 explained the CADA-PRO score ($R^2=64\%$).

361
362

363 Sensitivity to change

364 At the 12-month assessments (N=51), the patients' CADA-PRO total score had decreased of
365 1.53 points on average (SD=10.13, $p=0.286$, ES=-0.15). For patients with CADASIL (N=23), the score had
366 increased of 0.74 points on average (SD=10.35), $p=0.735$, ES=0.07), and for patients with other diagnoses
367 (N=28), it had decreased by 3.39 points (SD=9.74), $p=0.0763$, ES=-0.35). Of the 26 patients who
368 completed the PGIC, seven reported that their condition worsened, 10 perceived no change, and nine
369 reported an improvement of their condition.

370
371

372 **DISCUSSION**

373
374 The results of this study show that key outcomes experienced in daily life can be reported by
375 patients at early or intermediate stage of a cSVD using a simple questionnaire limited to fewer than 20
376 questions. This instrument was developed in individuals with ischemic cSVD, either sporadic or genetic,
377 including CADASIL patients. As the final tool was particularly fitted for CADASIL patients, it was named
378 CADA-PRO (CADASIL patient reported outcome). To our knowledge, this is the first instrument that can
379 help measure, in a comprehensive manner, the cognitive, motor, emotional and behavioral impact of a
380 cSVD on the quality of life, as perceived by the patients themselves. Different PRO measures have been
381 previously developed for stroke patients. Some of these tools were strongly focused on deficits
382 encountered after large cerebrovascular lesions not related to cSVD²⁶. Others were prepared for
383 evaluating specific services²⁷, such as rehabilitation, after persisting stroke deficits. Various
384 multidimensional tools, such as the Newcastle Stroke-Specific Quality of Life Measure²⁸, were found
385 unrelated to the family support or treatment effect. Finally, even the Stroke-PROM²⁹, one of the most
386 comprehensive measure, was validated only in elderly individuals and included questions related to
387 physical deficits that are not relevant to cSVD. Thus, none of the existing tools designed for
388 cerebrovascular diseases was specifically built on the complaints of patients with cSVD, as proposed
389 herein.

390 In the present study, the administration of the final 18-items CADA-PRO tool showed few missing
391 data, no ceiling or floor effect, and an excellent internal consistency. We identified four main dimensions
392 with significant impact from the patient's point of view, corresponding to the 4-domain structure of the scale,
393 assessing 1-disturbances in common activities of daily life, 2-attention and executive function deficit, 3-
394 reduced walking ability, and finally 4-anxiety and depression. Most items of the CADA-PRO tool were
395 focused on executive dysfunction, mood and behavior, rather than late symptoms such as dementia or
396 motor dependency, as they were developed for and by individuals recruited in consultations or short-term
397 hospitalization, who were able to complete the questionnaires themselves. Consequently, the CADA-PRO
398 should not be considered as a tool that summarizes all potential consequences of a cSVD, but rather as
399 one that captures the main difficulties experienced by the patient before the latest disease stage. As
400 anosognosia is expected to appear very late in the course of a cSVD, focusing on patients at early or
401 intermediate disease stage also proved reasonable. Moreover, these subjects represent the most relevant
402 target for testing preventive therapeutic interventions long before the occurrence of dependency.
403 Furthermore, the CADA-PRO questionnaire presents a good test-retest reliability, but responses to some
404 items could vary when the questionnaire was administered at hospital or one month later at home. In
405 practice, the questionnaire should be administered in a constant environment for obtaining the best

406 reliability. Finally, no significant change in patients' perceived condition between inclusion and the one-year
407 follow-up was observed neither using CADA-PRO score nor the PGCI. These results indicate that the
408 patients included in the study did not experience a clear worsening of their disease over one year, in line
409 with the relatively slow progression of the disease. Thus, a larger sample size and longer follow-up would
410 be required to answer the key question of how patients perceive the progression of their disease.

411 An important finding of our study concerns the contrasting results obtained in CADASIL patients
412 and in those having a different cSVD. In CADASIL patients, the CADA-PRO total score was significantly
413 correlated with the Rankin score, the SAS, HAD scores, Working Memory Index as well as TMT times. The
414 Anxiety-Depression sub-score was significantly correlated with the HAD and SAS scores, reflecting mood
415 alterations and apathy respectively. In patients with cSVDs distinct from CADASIL, CADA-PRO score and
416 sub-scores significantly correlated only with the HAD and SAS scores. Altogether, these results indicate
417 that the CADA-PRO tool is well fitted for CADASIL patients to report key outcomes in strong agreement
418 with multiple facets of bedside clinical evaluation. Patients with other cSVDs furthermore showed some
419 differences from patients with CADASIL: older age at inclusion and diagnosis, worse performances in
420 several neuropsychological assessments. Additional questionnaire items, larger samples or further
421 investigations are likely needed for improving the PRO measure for other types of cSVD.

422 Finally, we found that the total CADA-PRO score was only weakly correlated with the different
423 cognitive scores. These results are consistent with the lack of association between the subjective cognitive
424 complaints and neuropsychological performances reported in 152 patients with white matter
425 hyperintensities.³⁰ They are also in agreement with the results of a meta-analysis showing only a weak link
426 between cognitive complaints and cognitive scores in the elderly³¹, and an independent effect of depressive
427 symptoms on cognitive performances.^{30,31} In CADASIL patients, the association of the CADA-PRO total
428 score with the working memory index was independent of the association with the HAD depression score.
429 Therefore, the emotional and behavioral impact of the disease appears to influence the patients' quality of
430 life in ways that are distinct from cognitive impairment. These emotional and behavioral symptoms should
431 not be overlooked, as in patients with Cerebral Small Vessel Disease, mood disturbances were shown to
432 be the first predictor of quality of life.³²

433 This study comprises several methodological strengths. The CADA-PRO questionnaire was
434 developed from real data, in close association with cSVD or CADASIL patients and their families, and with
435 experts having a long experience in the management of genetic or sporadic cSVD. Two samples of
436 patients were recruited, with an acceptable number of individuals affected by a rare disease. Development
437 and validation of the tool followed the latest recommendations for the development of PRO measures,
438 investigating a wide range of psychometric properties. The present study also suffers from several
439 limitations. The questionnaire was initially developed with the CADASIL family association. This might
440 prevent obtaining a PROs instrument enabling to cover all potential phenotypic aspects of multiple sporadic
441 or genetic cSVDs. Moreover, a caregiver version of the CADA-PRO could not be developed, as caregivers
442 were missing in 30% of our development sample. Further development of a caregiver-reported outcome
443 using a larger sample would be promising. Our development study also showed that disagreement
444 between patient and caregiver was significantly higher when the average CADA-PRO score increased,
445 suggesting that anosognosia may develop in some patients as the disease progresses. This is consistent
446 with previous results showing that informant-reported cognitive complaints, but not patient-reported
447 cognitive complaints, correlate with white matter hyperintensities volume and functional abilities in cSVD
448 patients.³⁰ Furthermore, our tool would benefit from assessing its correlation with another scale measuring
449 quality of life. A last limitation is that the CADA-PRO questionnaire was developed in French and should
450 now be translated and further validated for its worldwide use.

451 In summary, the CADA-PRO tool can now be used in CADASIL patients to assess patient-
452 perceived impact of their disease in cross-sectional and longitudinal studies. This instrument is largely
453 validated and appears now suitable to provide additional secondary endpoints for future clinical trials.

454 Additional efforts are also needed to develop a caregiver version of PROs in CADASIL from the present
455 instrument.
456
457
458

459 **Acknowledgment**

460
461 We thank the team in charge of formatting and cleaning the database Mrs Claire Pacheco; Mr
462 Abbas Taleb for managing and collecting the data; Mrs Solange Hello and Celine Martin who managed and
463 organised the appointment of multiple family members involved in the present study; Mrs Nathalie
464 Gastelier, the research manager in charge of the Cohort Study. We also thank the CADASIL France
465 Association for their participation and permanent support (non-financial).

466
467 **Funding**

468 This research was mainly supported by the ANR grant RHU TRT_cSVD (ANR:16-RHUS-0004).
469 The study was also done with the help of the Association ARNEVA (Association de Recherche en
470 Neurologie Vasculaire).

471
472 **Disclosure**

473 HC reports grants from the Agence Nationale de la Recherche (French National Research
474 Agency).

475
476 **Supplementary Materials**

477 Tables S1–S7
478 Figure S1–S4

479 **References**

- 480
- 481 1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to
482 therapeutic challenges. *Lancet Neurol.* 2010;9:689–701.
- 483 2. Mancuso M, Arnold M, Bersano A, Burlina A, Chabriat H, Debette S, Enzinger C, Federico A, Filla
484 A, Finsterer J, et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus
485 recommendations of the European Academy of Neurology. *Euro J of Neurology.* 2020;27:909–927.
- 486 3. Chabriat H, Joutel A, Tournier-Lasserre E, Bousser MG. CADASIL: yesterday, today, tomorrow.
487 *Euro J of Neurology.* 2020;27:1588–1595.
- 488 4. Dupré N, Gueniot F, Domenga-Denier V, Dubosclard V, Nilles C, Hill-Eubanks D, Morgenthaler-
489 Roth C, Nelson MT, Keime C, Danglot L, et al. Protein aggregates containing wild-type and mutant
490 NOTCH3 are major drivers of arterial pathology in CADASIL. *J Clin Invest.* 2024;134:e175789.
- 491 5. Razvi SSM. The prevalence of cerebral autosomal dominant arteriopathy with subcortical infarcts
492 and leucoencephalopathy (CADASIL) in the west of Scotland. *J Neurol Neurosurg Psychiatry.*
493 2005;76:739–741.
- 494 6. Chabriat H, Vahedi K, Bousser MG, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, Tournier Lasserre
495 E, Krebs MO, Julien J, et al. Clinical spectrum of CADASIL: a study of 7 families. *Lancet.* 1995;346:934–
496 939.
- 497 7. Bradley C. Feedback on the FDA’s February 2006 draft guidance on Patient Reported Outcome
498 (PRO) measures from a developer of PRO measures. *Health Qual Life Outcomes.* 2006;4:78.
- 499 8. European Medicines Agency. Regulatory Science to 2025 - EMA/110706/2020. 2020. Available at
500 [https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf)
501 [strategic-reflection_en.pdf](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf).
- 502 9. US Food and Drug Administration. Patient-reported outcome measures: use in medical product
503 development to support labeling claims. 2009. Available at <https://www.fda.gov/media/77832/download>.
- 504 10. Gagnier JJ, Lai J, Mokkink LB, Terwee CB. COSMIN reporting guideline for studies on
505 measurement properties of patient-reported outcome measures. *Qual Life Res.* 2021;30:2197–2218.
- 506 11. Ferris SH. General Measures of Cognition. *Int Psychogeriatr.* 2003;15:215–217.
- 507 12. Madureira S, Verdelho A, Ferro J, Basile A-M, Chabriat H, Erkinjuntti T, Fazekas F, Hennerici M,
508 O’Brien J, Pantoni L, et al. Development of a neuropsychological battery for the Leukoaraiosis and
509 Disability in the Elderly Study (LADIS): experience and baseline data. *Neuroepidemiology.* 2006;27:101–
510 116.
- 511 13. Peters N, Opherk C, Danek A, Ballard C, Herzog J, Dichgans M. The Pattern of Cognitive
512 Performance in CADASIL: A Monogenic Condition Leading to Subcortical Ischemic Vascular Dementia.
513 *AJP.* 2005;162:2078–2085.
- 514 14. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. *Nat Protoc.*
515 2006;1:2277–2281.
- 516 15. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making
517 test: normative values from 287 normal adult controls. *Ital J Neurol Sci.* 1996;17:305–309.
- 518 16. Berg EA. A simple objective technique for measuring flexibility in thinking. *J Gen Psychol.*
519 1948;39:15–22.
- 520 17. Weschler D. WMS-III administration and scoring manual. San Antonio, Texas: Psychological
521 Corporation; 1997.
- 522 18. Grober E, Lipton RB, Hall C, Crystal H. Memory impairment on free and cued selective reminding
523 predicts dementia. *Neurology.* 2000;54:827–832.
- 524 19. Epelbaum S, Benisty S, Reyes S, O’Sullivan M, Jouvent E, Düring M, Hervé D, Opherk C,
525 Hernandez K, Kurtz A, et al. Verbal memory impairment in subcortical ischemic vascular disease: a
526 descriptive analysis in CADASIL. *Neurobiol Aging.* 2011;32:2172–2182.
- 527 20. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, Studenski S, Berkman LF,
528 Wallace RB. Lower extremity function and subsequent disability: consistency across studies, predictive
529 models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A*

530 *Biol Sci Med Sci.* 2000;55:M221-231.

531 21. Zigmund AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Neurol Scand.*
532 1983;67:361–370.

533 22. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability,
534 validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.*
535 1992;4:134–139.

536 23. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of
537 daily living. *Gerontologist.* 1969;9:179–186.

538 24. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective
539 outcome measures. *J Manipulative Physiol Ther.* 2004;27:26–35.

540 25. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The
541 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for
542 reporting observational studies. *Journal of Clinical Epidemiology.* 2008;61:344–349.

543 26. Hilari K, Byng S, Lamping DL, Smith SC. Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39):
544 Evaluation of Acceptability, Reliability, and Validity. *Stroke.* 2003;34:1944–1950.

545 27. McCormick S, Jarvis JM, Terhorst L, Richardson A, Kaseman L, Kesbhat A, Yepuri Y, Beyene E,
546 VonVille H, Bendixen R, et al. Patient-report and caregiver-report measures of rehabilitation service use
547 following acquired brain injury: a systematic review. *BMJ Open.* 2024;14:e076537.

548 28. Buck D, Jacoby A, Massey A, Steen N, Sharma A, Ford GA. Development and Validation of
549 NEWSQOL®, the Newcastle Stroke-Specific Quality of Life Measure. *Cerebrovasc Dis.* 2004;17:143–152.

550 29. Alexander SK, Brown JM, Graham A, Nestor PJ. CADASIL presenting with a behavioural variant
551 frontotemporal dementia phenotype. *J Clin Neurosci.* 2014;21:165–167.

552 30. Arola A, Laakso HM, Heinonen H, Pitkänen J, Ahlström M, Lempiäinen J, Paajanen T, Virkkala J,
553 Koikkalainen J, Lötjönen J, et al. Subjective vs informant-reported cognitive complaints have differential
554 clinical significance in covert cerebral small vessel disease. *Cereb Circ Cogn Behav.* 2023;5:100182.

555 31. Burmester B, Leathem J, Merrick P. Subjective Cognitive Complaints and Objective Cognitive
556 Function in Aging: A Systematic Review and Meta-Analysis of Recent Cross-Sectional Findings.
557 *Neuropsychol Rev.* 2016;26:376–393.

558 32. Brookes RL, Willis TA, Patel B, Morris RG, Markus HS. Depressive Symptoms as a Predictor of
559 Quality of Life in Cerebral Small Vessel Disease, Acting Independently of Disability; a Study in Both
560 Sporadic Small Vessel Disease and Cadasil. *Int J Stroke.* 2013;8:510–517.

561

562

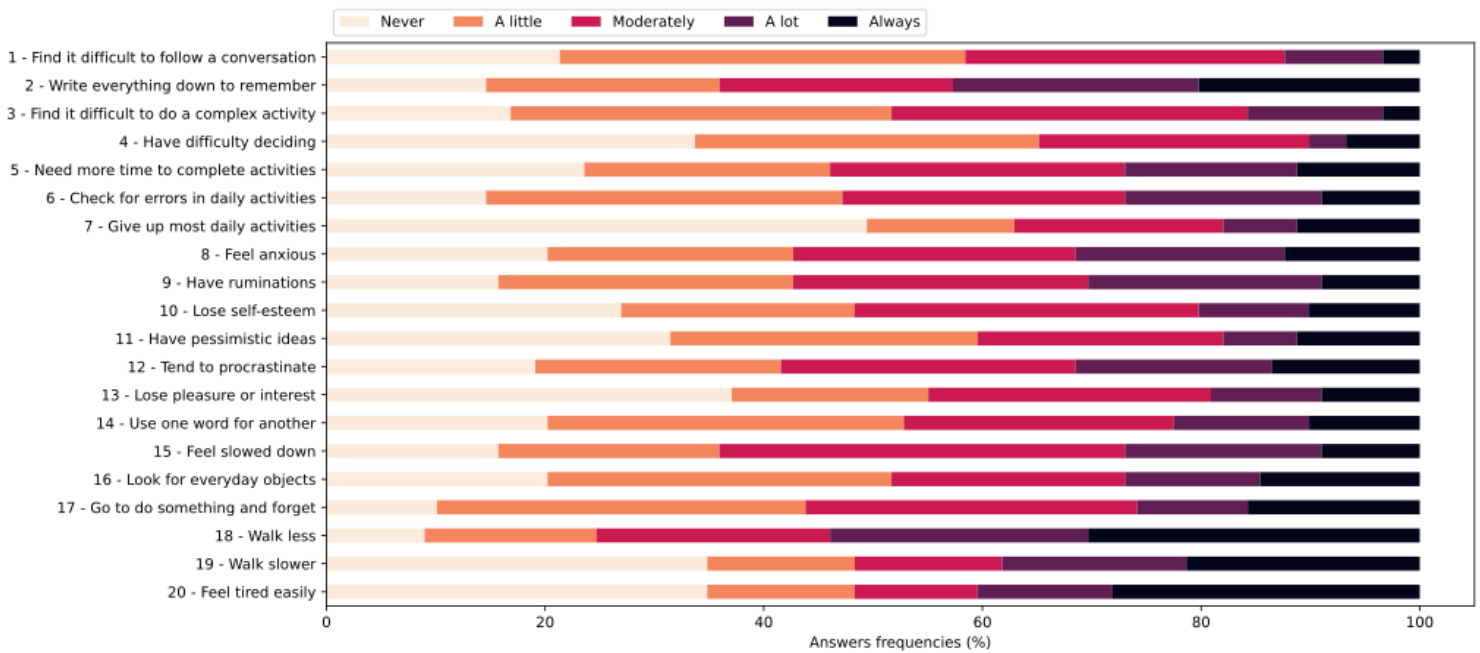
563 **FIGURES AND TABLES**

564 **FIGURES**

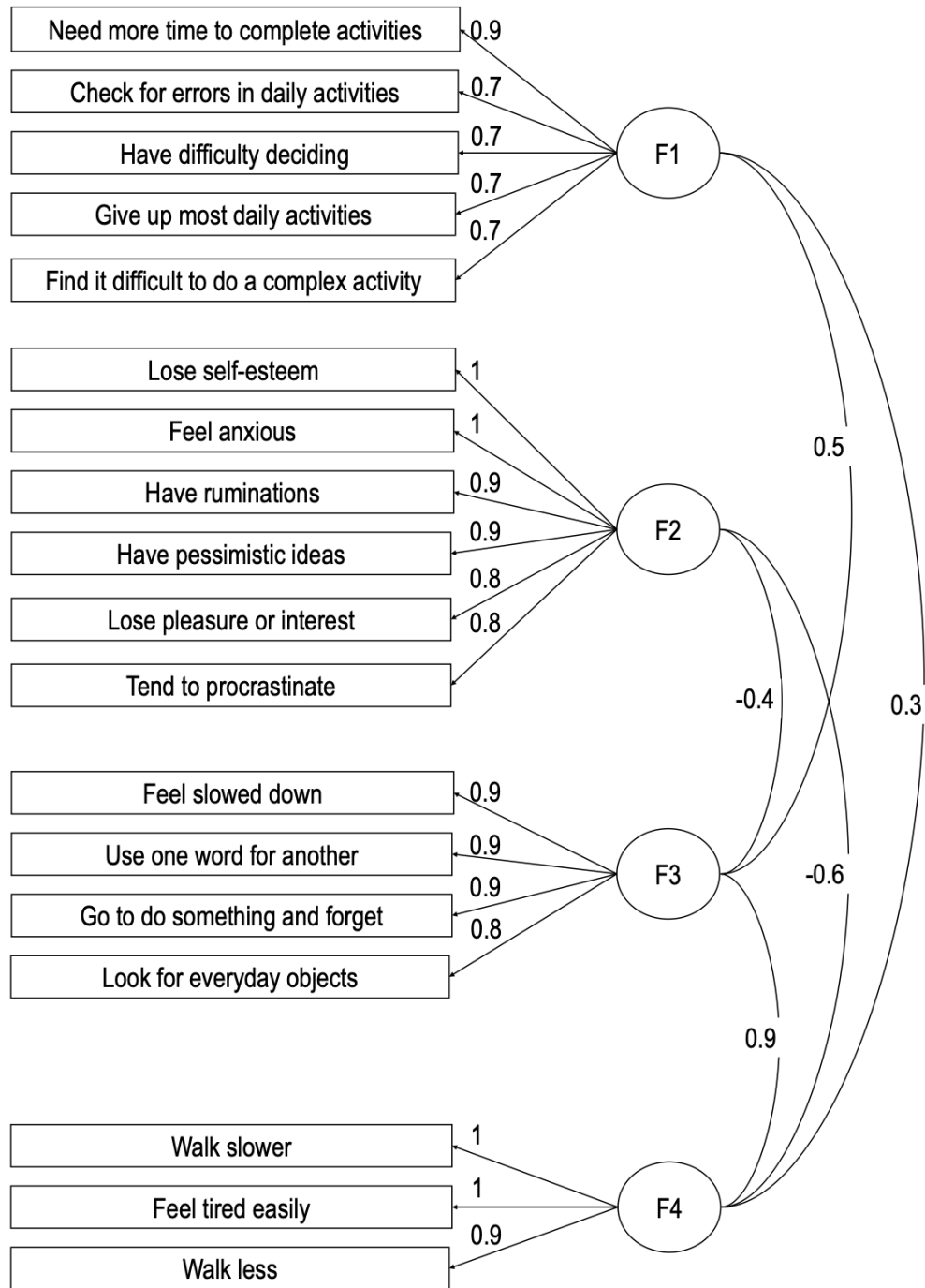
565

566

567 **Figure 1:** Frequencies of answers at inclusion visit for the selection of items composing the
568 validation-study version of CADA-PRO (N=89)
569



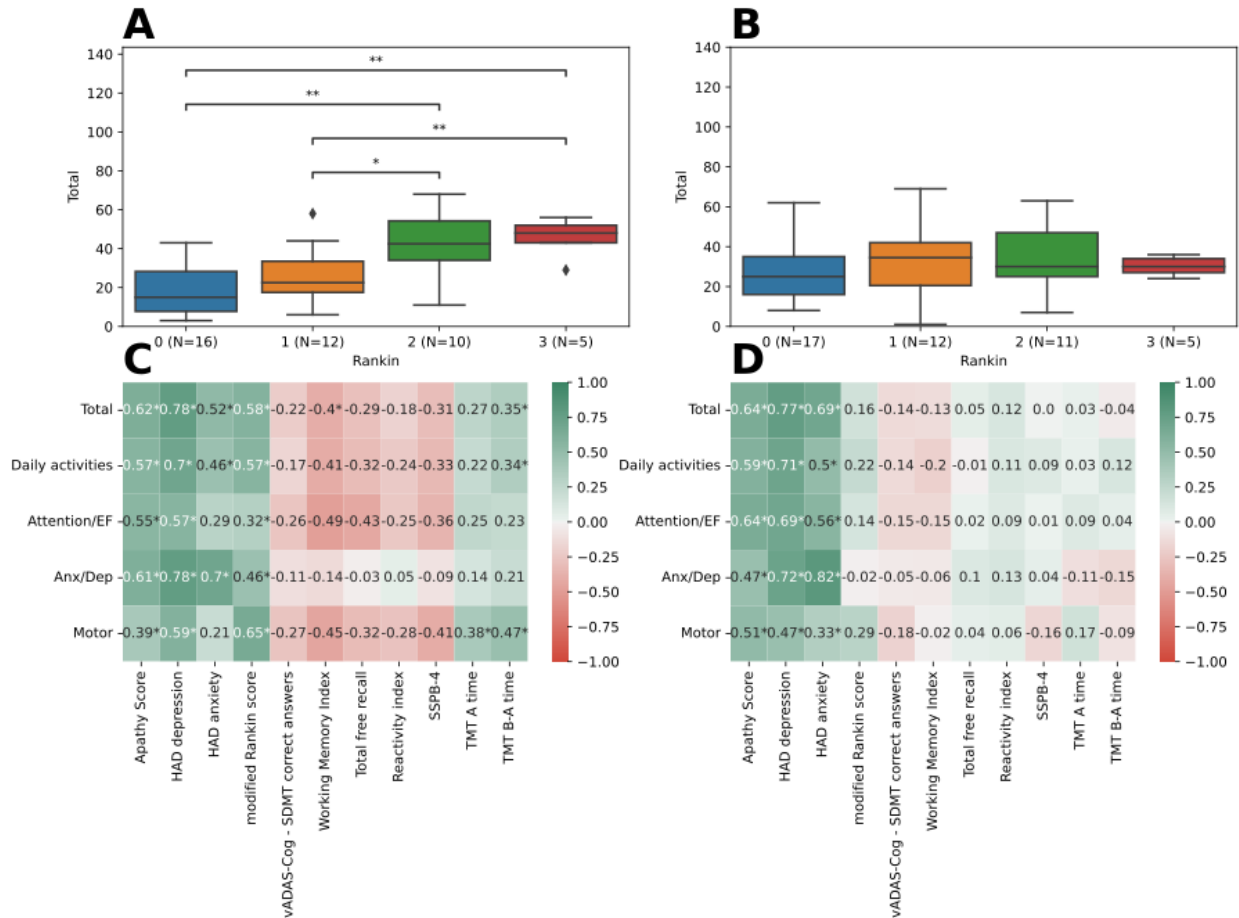
570 **Figure 2: Item loadings and factor correlations for the validation-study version of the CADA-PRO**
 571 **(18-items).**
 572 The data are shown after VARIMAX rotation. F1, F2, F3 and F4 are the four identified factors. They are
 573 labelled as follows: F1=Impact on daily activities, F2=Anxiety/depression, F3=Attention/EF, F4=Motor.



574

575 **Figure 3: Correlations between the CADA-PRO scores and different clinical scores in patients with**
 576 **CADASIL (A, C) and patients with other types of cSVD (B, D)**

577 A and B: Relationships between that CADA-PRO total score and the Rankin score in CADASIL patients (A)
 578 or in patients with another cSVD (B). Significance stars are plotted only in presence of a significant
 579 difference between the different levels of the Rankin score. C and D: Pearson correlation coefficients
 580 computed between the different CADA-PRO sub-scores and different clinical scores in patients with
 581 CADASIL (C) and in those with other cSVDs (D). The CADA-PRO total score is labelled as Total, the
 582 Anxiety/Depression sub-score as Anx/Dep, the Impact on Daily Activities sub-score as Daily Activities.
 583 Significance stars are plotted only for significant correlations. Statistical significance is indicated as *:
 584 0.01<p<=0.05; **: 0.001<p<=0.01; ***: 0.0001<p<=0.001; ****: p<=0.0001.
 585



586
587

588 TABLES

589

590

591 **Table 1: Characteristics at baseline of the participants**

592

	Development study (N=44)	Validation study (N=89)
Age at inclusion	62.8±10.5	60.5±13.0
Sex: Male	28 (63.6%)	45 (50.6%)
Education>=High School Diploma	31 (70.5%)	59 (66.3%)
DIAGNOSIS		
CADASIL	1 (2.3%)	43 (48.3%)
Other cSVD	43 (97.7%)	46 (51.7%)
- Genetic	7	6
- Non-genetic	36	40
CLINICAL MANIFESTATIONS		
Positive stroke history	27 (61.4%)	36 (40.9%)
Time since diagnosis (y) (0/100)	4.0±4.8	6.1±5.9
CLINICAL SCORES		
modified Rankin score (0/6)		
- 0	24 (58.5%)	29 (32.6%)
- 1	9 (22.0%)	28 (31.5%)
- 2	5 (12.2%)	21 (23.6%)
- 3	3 (7.3%)	10 (11.2%)
Apathy Score (0/42)	12.8±6.1	12.8±5.6
vADAS-Cog – SDMT correct answers (0/110)	32.6±10.9	34.6±12.7
Reactivity index (0/100)	85.9±14.4	87.5±16.6
Total free recall (0/48)	26.7±7.7	27.4±8.6
HAD depression (0/21)	4.3±3.5	5.4±4.5
HAD anxiety (0/21)	6.4±3.9	7.9±4.2
Working Memory Scale	/	96.4±16.1
SSPB-4 (0/4)	2.9±1.6	3.7±0.7
TMT A time (0/180)	45.8±20.0	44.2±23.9
TMT B time (0/300)	128.0±78.9	112.5±72.1
CADA-PRO		
CADA-PRO total (0/72)	/	30.2±16.7
CADA-PRO Impact on daily activities (0/20)	/	7.3±4.9
CADA-PRO Anxiety-depression (0/24)	/	9.8±6.4
CADA-PRO Attention-EF (0/16)	/	7.0±4.0
CADA-PRO Motor (0/12)	/	6.1±4.0

593

594

595

596 **Table 2: Internal consistency and test-retest reliability of the final CADA-PRO total score and its**
597 **four sub-scores.**

598 Internal consistency is assessed by Cronbach's alpha (N=89). Test-retest reliability (N=64) is assessed by
599 Intraclass correlation coefficient (ICC), Standard Error of Measurement (SEM) and Smallest Detectable
600 Change (SDC).
601

Scores	Alpha	ICC	SEM	SDC
Total (0/72)	0.95(0.92;0.97)	0.88(0.80;0.92)	5.95(4.78;7.56)	2.06(1.66;2.62)
Anx/Dep (0/24)	0.91(0.87;0.95)	0.88(0.80;0.92)	2.37(1.90;3.01)	0.82(0.66;1.04)
Attention/EF (0/16)	0.84(0.75;0.90)	0.69(0.53;0.80)	2.21(1.77;2.70)	0.77(0.61;0.94)
Daily Activities (0/20)	0.87(0.80;0.92)	0.82(0.72;0.89)	2.09(1.65;2.62)	0.72(0.57;0.91)
Motor (0/12)	0.85(0.77;0.91)	0.80(0.70;0.88)	1.76(1.38;2.19)	0.62(0.46;0.76)

602
603

604 **Supplementary Material**

605

606 **Figure S1:** Flowchart illustrating items selection.

607

608 **Figure S2:** Frequencies of answers for the items of the development study of CADA-PRO.

609

610 **Figure S3:** Agreement between information collected in patients and caregivers.

611

612 **Figure S4:** Pearson correlation coefficients between clinical scores.

613

614 **Table S1:** Characteristics at baseline of the participants at each step of the study.

615

616 **Table S2:** Development and validation versions of CADA-PRO items (numbers and labels)

617

618 **Table S3:** Unrotated factor loadings of the development and validation versions of CADA-PRO

619

620 **Table S4:** Characteristics of participants with CADASIL or another cSVD at inclusion in the
621 validation study (significant differences are shown in BOLD)

622

623 **Table S5:** Final version of CADA-PRO, with instructions.

624

625 **Table S6:** Internal consistency, test-retest reliability, and proportion of explained variance for the 18
626 items of the final CADA-PRO.

627

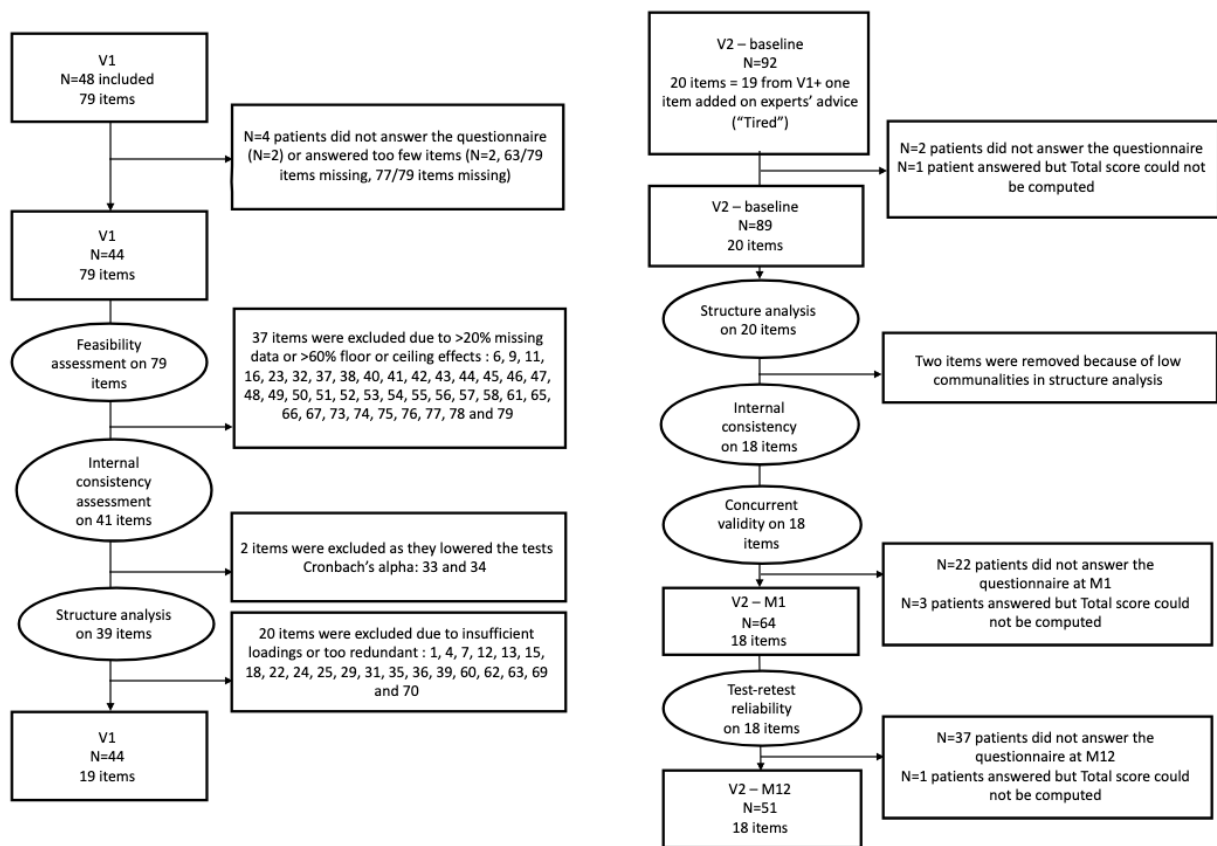
628 **Table S7:** Multiple regression of CADA-PRO total score on clinical variables that were selected by a
629 stepwise variable selection.

630

631

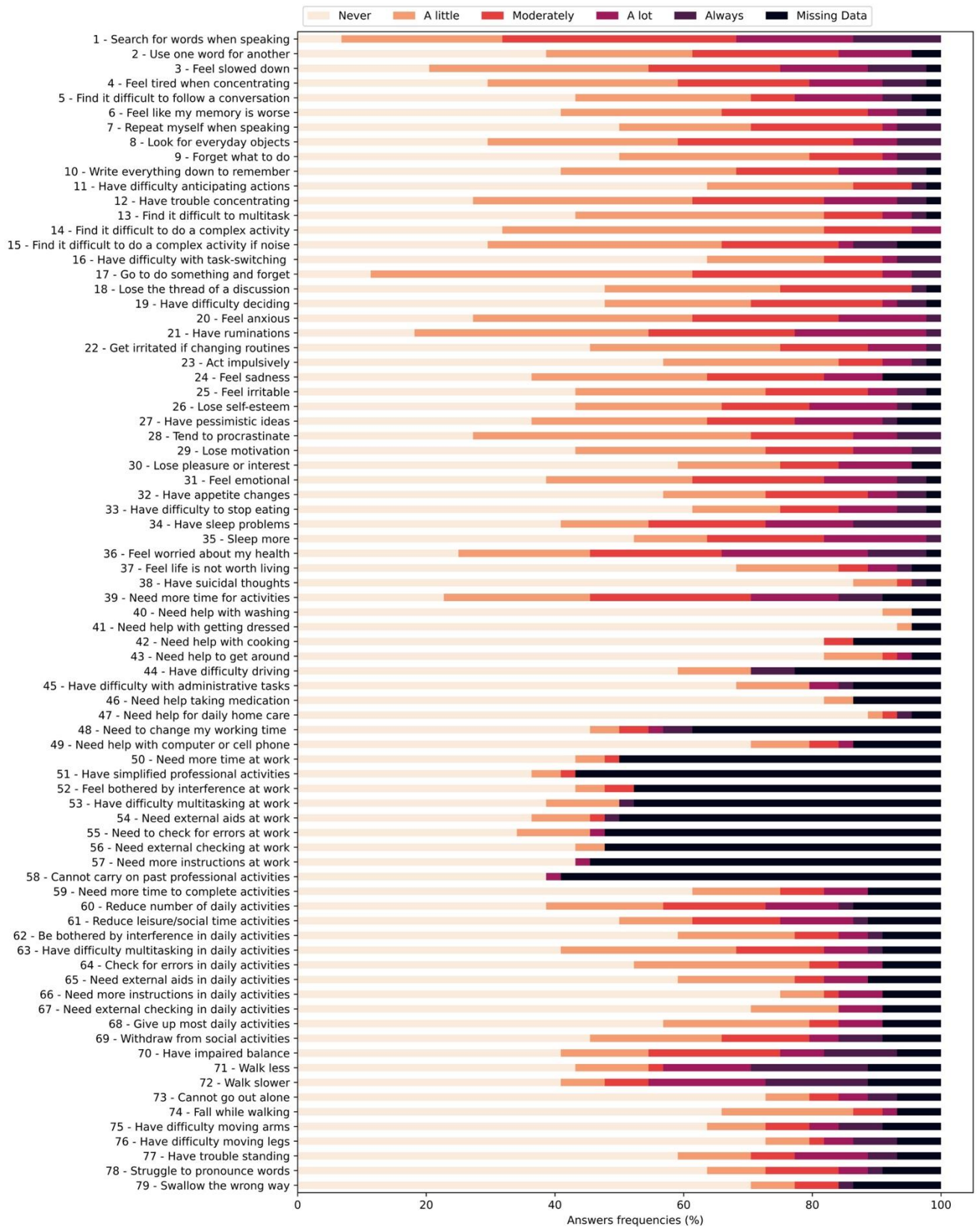
632

633 **Figure S1: Flowchart illustrating items selection.**
 634 Legend: all items selection steps, from the development version (“v1”) to the validation version (“v2”), at
 635 baseline, one-month follow-up (M1), and 12-months follow-up (M12).
 636 Note on questionnaire acceptability: In the development version of CADA-PRO, patients were also asked if
 637 he questionnaire as a whole was 1) understandable, 2) accurately and 3) exhaustively represented their
 638 everyday difficulties with the disease, 4) could be answered without assistance, and 5) were emotionally
 639 difficult to answer. Patients were also prompted to give items that did not fit the criteria in free text spaces.
 640 Only one patient pointed out that a specific item was difficult to answer, and this item (the 39th) had already
 641 been removed due to insufficient loading in the structure analysis. As 35/41 patients found that the
 642 questions were easy to understand, 35/40 found that they accurately represented their difficulty, 34/40
 643 found that the questionnaire was exhaustive, 34/40 that it could be answered without help, and 32/40 that it
 644 was not emotionally difficult to answer, we considered the questionnaire, as a whole, was satisfactory on
 645 these points.
 646



647
 648
 649
 650

651 **Figure S2: Frequencies of answers for the items of the development study of CADA-PRO.**
 652 **Legend:** Answers obtained from the 44 participants included in the development study are detailed.



653
 654
 655
 656
 657

658 **Figure S3: Agreement between information collected in patients and caregivers.**

659
 660 Legend: Caregivers scores disagree with those of patients on different items selected in the development
 661 study. Caregivers tend to give more severe responses compared to patients. This disagreement between
 662 caregivers and patients increases with disease severity computed as the mean score.
 663

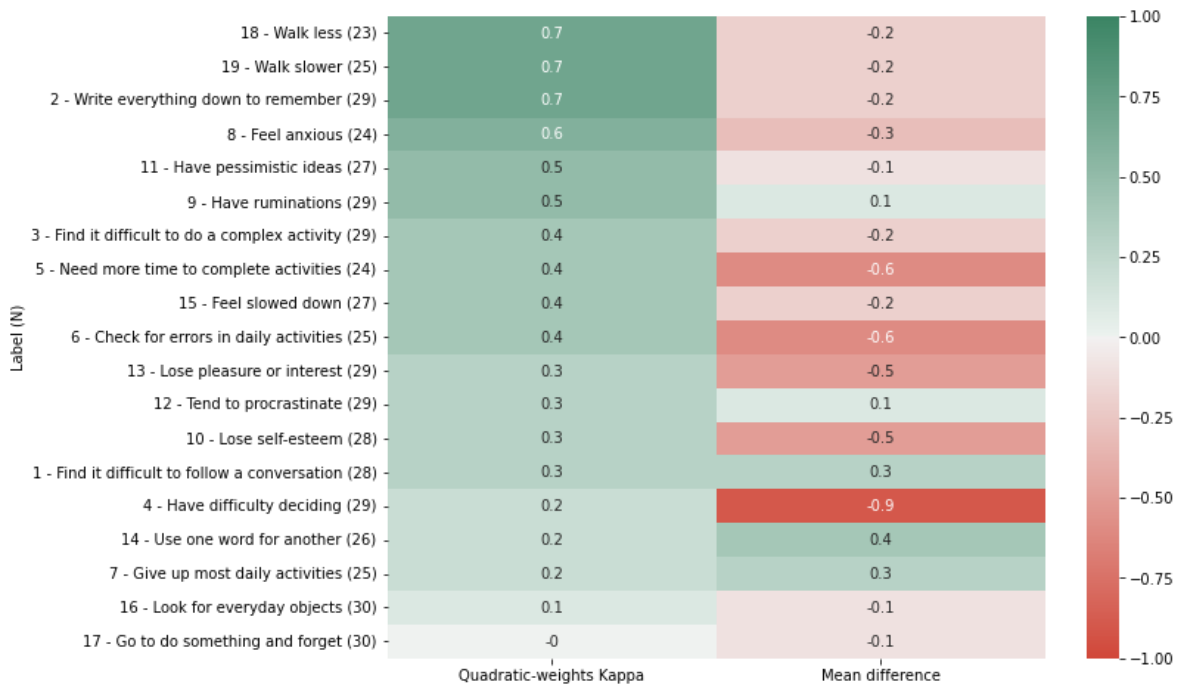
664 **3A: Agreement between patients and caregiver CADA-PRO item scores obtained during the**
 665 **development study, using quadratic-weights kappa sorted in ascending order.**

666 Legend: The mean difference between patient and caregiver item score (from 0 – never has the problem to
 667 4 – always have the problem) is given for each item. A positive mean difference indicates that the caregiver
 668 gave a superior rating to that of the patient (i.e. the caregiver reported the patient to have the difficulty more
 669 often than is reported by the patient). The number of data used for comparison (answers obtained on both
 670 sides) is given in parenthesis for each item level.
 671

672 **3B: Bland-Altman plot displaying the difference between patient and caregiver scores according to**
 673 **the average difference score between patients and caregivers.**

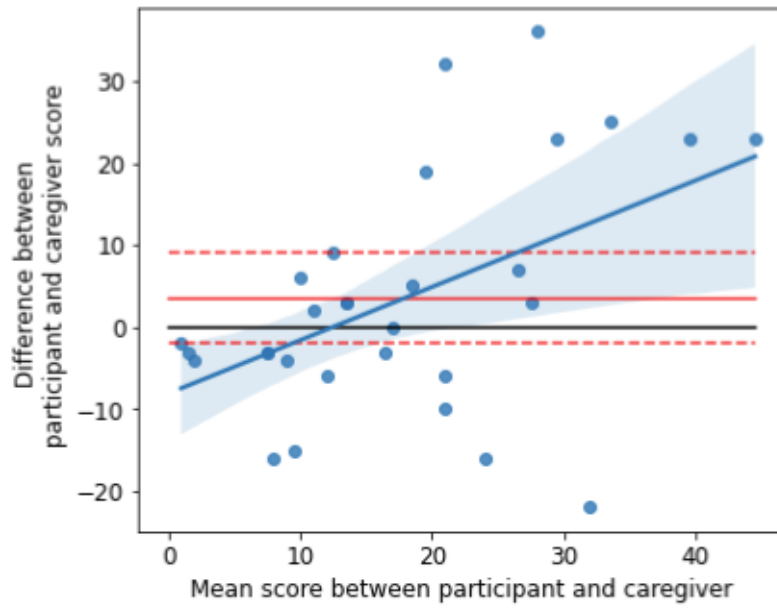
674 Legend: The trend line is represented in blue. The black horizontal line indicates a zero difference; the red
 675 line indicates the mean difference, with the red dotted line representing the mean difference confidence
 676 interval. This plot illustrates the significant correlation (Pearson $r=0.49$, $p=0.005$) between the mean score
 677 and the scores difference: the larger the average CADA-PRO score, the larger the discrepancy between
 678 the patient and their caregiver.
 679

680 **A**
 681



682
 683
 684

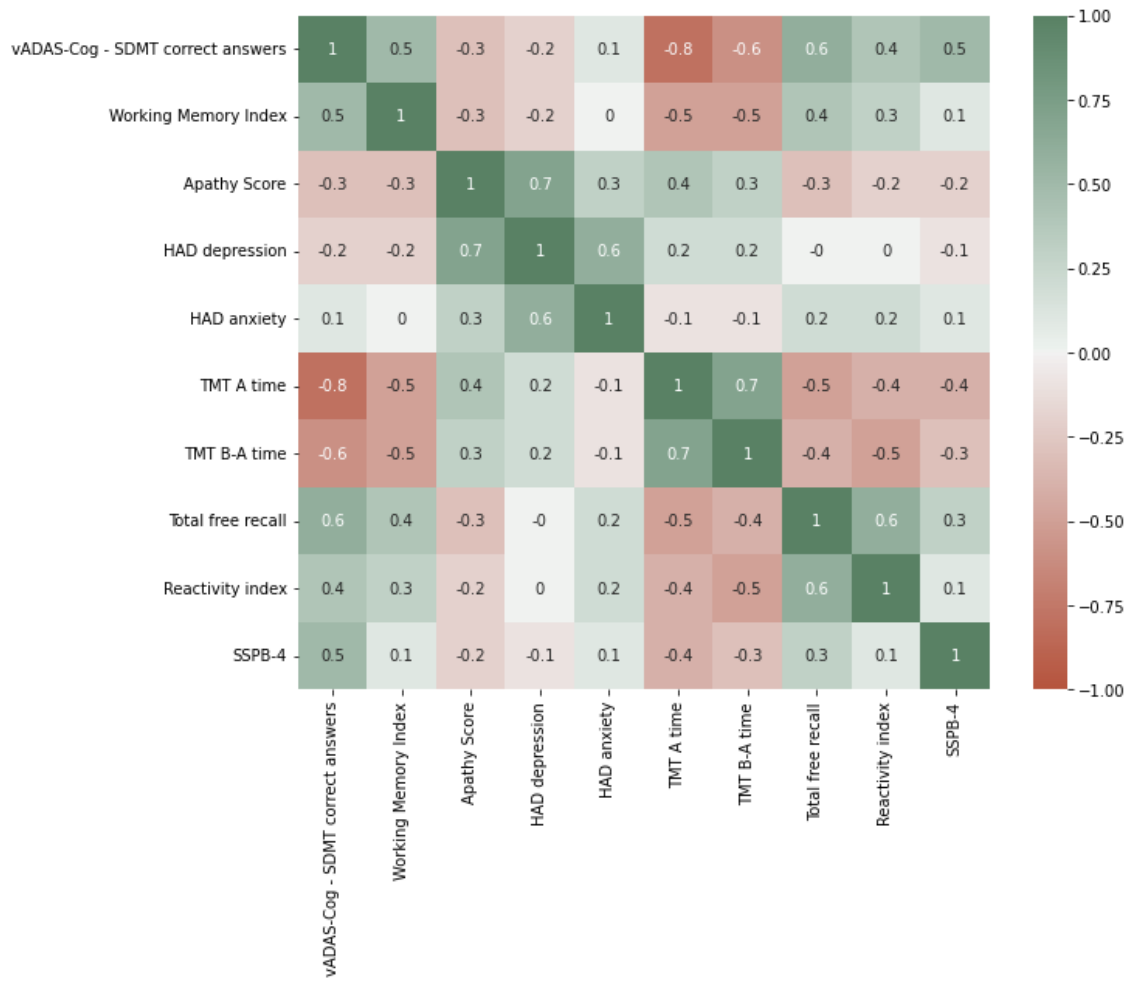
685 **B**
686



687
688

689
690
691

Figure S4: Pearson correlation coefficients between clinical scores.



692
693
694
695

Table S1: Characteristics at baseline of the participants at each step of the study.

	Development study	Validation study Inclusion	Validation study M1	Validation study M12
Number of subjects	44	89	64	51
Age at inclusion	62.8±10.5	60.5±13.0	59.2±12.1	60.7±13.1
Sex: Male	28 (63.6%)	45 (50.6%)	32 (50.0%)	27 (52.9%)
Laterality: Right-handed	38 (92.7%)	81 (92.0%)	57 (89.1%)	47 (94.0%)
	*1 NaN	*1 NaN		*1 NaN
Education>=High School Diploma	31 (70.5%)	59 (66.3%)	47 (73.4%)	38 (74.5%)
Evaluation context				
- One Day Hospital	21 (47.7%)	36 (56.2%)		
- Consultation	22 (50.0%)	27 (42.2%)		
- Extended hospitalization	1 (2.3%)	1 (1.6%)		
DIAGNOSIS				
CADASIL	1 (2.3%)	43 (48.3%)	33 (51.6%)	23 (45.1%)
Other cSVD	43 (97.7%)	46 (51.7%)	31 (48.4%)	28 (54.9%)
- HTRA1 related cSVD	0	3	3	3
- COL4A1/4A2 related cSVD	7	3	1	1
- Other non-genetic cSVD	36	40	27	24
CLINICAL MANIFESTATIONS				
Positive stroke history	27 (61.4%)	36 (40.9%)	26 (41.3%)	24 (48.0%)
- Ischemic Stroke	21 (77.8%)	31 (34.8%)	22 (34.4%)	21 (41.2%)
- Hemorrhagic Stroke	6 (22.2%)	7 (7.9%)	6 (9.4%)	4 (7.8%)
Age at Diagnosis (18/100)	58.8± 0.9	54.1±12.7	53.5±12.9	53.9±13.3
Time since diagnosis (y) (0/100)	4.0±4.8	6.1±5.9	6.1±6.1	6.5±7.1
CLINICAL SCORES				
modified Rankin score (0/6)				
- 0	24 (58.5%)	29 (32.6%)	23 (36.5%)	20 (40.0%)
- 1	9 (22.0%)	28 (31.5%)	21 (33.3%)	15 (30.0%)
- 2	5 (12.2%)	21 (23.6%)	14 (22.2%)	10 (20.0%)
- 3	3 (7.3%)	10 (11.2%)	5 (7.9%)	5 (10.0%)
Apathy Score (0/42)	12.8±6.1	12.8±5.6	12.6±5.8	12.5±5.4
vADAS-Cog – SDMT correct answers (0/110)	32.6±10.9	34.6±12.7	36.7±12.1	34.3±12.3
Reactivity index (0/100)	85.9±14.4	87.5±16.6	88.4±16.8	84.7±19.1
Total cued recall (0/48)	17.7±5.7	17.2±6.0	16.8±6.1	16.6±5.4
Total free recall (0/48)	26.7±7.7	27.4±8.6	28.0±8.7	27.1±8.6
HAD depression (0/21)	4.3±3.5	5.4±4.5	5.2±4.5	5.4±4.8
HAD anxiety (0/21)	6.4±3.9	7.9±4.2	8.0±4.2	7.6±4.7
iADL-current activities (0/8)	7.7±1.1	7.6±1.1	7.8±0.6	7.7±0.9
iADL-selfcare (0/6)	5.9±0.8	5.8±0.6	5.9±0.5	5.9±0.4
Working Memory Scale	/	96.4±16.1	98.3±16.2	97.2±16.4
SSPB-4 (0/4)	2.9±1.6	3.7±0.7	3.8±0.6	3.8±0.5
TMT A time (0/180)	45.8±20.0	44.2±23.9	41.1±20.8	43.9±25.3
TMT B errors (0/24)	2.4±5.3	0.9±1.7	0.9±1.8	1.0±2.0
TMT B time (0/300)	128.0±78.9	112.5±72.1	103.1±64.9	109.1±67.8
Wisconsin-completed categories (0/6)	4.8±1.4	5.2±1.4	5.4±1.2	5.3±1.4
Wisconsin-perseverations (0/47)	4.5±5.5	1.7±3.7	1.4±2.9	1.5±3.1
MRI LESIONS				
Microbleeds	12 (27.3%)	28 (31.5%)	22 (34.4%)	14 (27.5%)
Transient ischemic attack	1 (2.3%)	8 (9.0%)	5 (7.8%)	4 (7.8%)
Lacunae	17 (38.6%)	42 (47.2%)	31 (48.4%)	23 (45.1%)
WMH	41 (93.2%)	86 (96.6%)	63 (98.4%)	50 (98.0%)
CADA-PRO				
CADA-PRO total (0/72)	/	30.2±16.7	28.4±16.5	29.0±18.1
CADA-PRO Impact on daily activities (0/20)	/	7.3±4.9	6.8±4.8	6.7±5.6
CADA-PRO Anxiety-depression (0/24)	/	9.8±6.4	9.6±6.5	9.5±7.0
CADA-PRO Attention-EF (0/16)	/	7.0±4.0	6.5±3.9	6.8±4.1
CADA-PRO Motor (0/12)	/	6.1±4.0	5.5±4.0	6.0±4.2

698
699
700

Table S2: Development and validation versions of CADA-PRO items (full text, numbers and labels).
Legend: items full texts are given in a provisory English translation

Question in v1	Number in v1	Question in v2 if different from v1	Number in v2	Label
I often have the word on the tip of my tongue, I search for my words, and it makes it difficult for me to communicate, apart from proper nouns (people's names).	1	/	/	Search for words when speaking
I sometimes use one word for another	2	/	14	Use one word for another
I feel slowed down in the way I think and/or do things	3	/	15	Feel slowed down
I feel tired after trying to concentrate, which is new	4	/	/	Feel tired when concentrating
I don't always understand what's being said because the conversation goes too fast or there's too much information for me, even if I've heard what's being said.	5	/	1	Find it difficult to follow a conversation
I have the feeling that my memory is less efficient than that of people my age.	6	/	/	Feel like my memory is worse
Those around me tell me that I have things repeated or that I'm repeating myself because I forget what I've just been told.	7	/	/	Repeat myself when speaking
I waste a lot of time looking for small everyday objects.	8	/	16	Look for everyday objects
I have difficulty remembering what I have to do (for example appointments, taking medication, managing paperwork...).	9	/	/	Forget what to do
I have to write everything down so that I don't forget	10	/	2	Write everything down to remember
I have difficulty anticipating the consequences of certain actions and find myself in trouble afterwards (for example, if I'm late for an appointment, I wouldn't think of taking the phone number to let people know).	11	/	/	Have difficulty anticipating actions
I have trouble concentrating	12	/	/	Have trouble concentrating
I have difficulty multitasking (e.g. driving and following a conversation at the same time).	13	/	/	Find it difficult to multitask
I find it difficult to do a complex activity; I may forget a step and/or lose the thread.	14	/	3	Find it difficult to do a complex activity
In the presence of background noise (noise from the radio, people talking nearby...), I have difficulty performing a complex activity.	15	/	/	Find it difficult to do a complex activity if noise
I find it difficult to switch effortlessly from one activity to another (e.g. dealing with paperwork and answering the phone immediately).	16	/	/	Have difficulty with task-switching
I sometimes go into a room to do something and then can't remember what it was.	17	/	17	Go to do something and forget
I sometimes lose the thread of a discussion with several people, even if I hear them clearly.	18	/	/	Lose the thread of the discussion

I find it hard to make decisions when I had no problem doing so before.	19	/	4	Have difficulty deciding
I feel anxious, nervous and have difficulty relaxing.	20	/	8	Feel anxious
I tend to brood and worry.	21	/	9	Have ruminations
I get irritated if my routines/habits are changed	22	/	/	Get irritated if changing routines
I act without thinking and impulsively compared to my habits.	23	/	/	Act impulsively
I feel sad.	24	/	/	Feel sadness
I'm irritable, moody, impatient and quick-tempered.	25	/	/	Feel irritable
I've lost my self-esteem.	26	/	10	Lose self-esteem
I have pessimistic ideas and I'm discouraged about my future.	27	/	11	Have pessimistic ideas
I feel weary, it takes more effort to get started and I tend to procrastinate.	28	/	12	Tend to procrastinate
I've lost the desire to do things, I lack motivation and as a result I'm doing fewer things.	29	/	/	Lose motivation
I've lost the pleasure or interest in some of the things I used to enjoy.	30	/	13	Lose pleasure or interest
I feel very emotional, on edge	31	/	/	Feel emotional
My appetite has changed, I've lost weight or gained weight without wanting to.	32	/	/	Have appetite changes
I have difficulty limiting myself when eating sweets or my favourite foods.	33	/	/	Have difficulty to stop eating
I have sleep problems: difficulty falling asleep or waking up during the night (apart from visits to the toilet after which I quickly go back to sleep).	34	/	/	Have sleep problems
I sleep more.	35	/	/	Sleep more
I'm worried about my health/what's happening to me.	36	/	/	Feel worried about my health
I sometimes think life isn't worth living.	37	/	/	Feel life is not worth living
I have suicidal thoughts.	38	/	/	Have suicidal thoughts
I need more time to do what I used to do.	39	/	/	Need more time for routine activities
I need help to wash myself.	40	/	/	Need help with washing
I need help getting dressed.	41	/	/	Need help with getting dressed
I need help with cooking.	42	/	/	Need help with cooking
I need help to get around by foot or by public transport (because I get lost, I'm afraid of the unexpected...).	43	/	/	Need help to get around
I have difficulty driving (I lose my cool when faced with unexpected events, I've had accidents...).	44	/	/	Have difficulty driving
I have difficulty managing my finances and/or administrative paperwork (taxes, bank	45	/	/	Have difficulty with administrative tasks

accounts, social security, etc.).				
I need help taking my medication.	46	/	/	Need help taking medication
I need help with daily housework and maintenance (e.g.: I forget things when I clean, I forget steps when I tinker...).	47	/	/	Need help for daily home care
I have an arrangement of my working time	48	/	/	Need to change my working time
I now need help to use my computer and/or cell phone.	49	/	/	Need help with computer or cell phone
I have difficulties in my professional activities: I need more time to complete them.	50	/	/	Need more time at work
I have difficulties in my professional activities: I have simplified the tasks I can do	51	/	/	Have simplified professional activities
I have difficulties in my professional activities: I am bothered by interference (I am disturbed if there is noise around me or if I am solicited...).	52	/	/	Feel bothered by interference at work
I have difficulties in my professional activities: I can't multitask as I used to.	53	/	/	Have difficulty multitasking at work
I have difficulties in my professional activities: I need more external aids (e.g. diaries, Smartphone, paper notes...)	54	/	/	Need external aids at work
I have difficulties in my professional activities: I need to check that I haven't made any mistakes.	55	/	/	Need to check for errors at work
I have difficulties in my professional activities: I need someone to check that I haven't made any mistakes.	56	/	/	Need external checking at work
I have difficulties in my professional activities: Someone needs to tell me what to do and how to do it, because I'm having trouble getting organized.	57	/	/	Need more instructions at work
I have difficulties in my everyday activities (for example: leisure, social and family life...): I had to be reassigned or I can no longer carry out my professional activity.	58	/	/	Cannot carry on past professional activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I need more time to complete them	59	I have difficulties in my everyday and/or professional activities: I need more time to complete them	5	Need more time to complete activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I reduced the number of my activities compared to before	60	/	/	Reduce number of daily activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I reduced the time I spend on them	61	/	/	Reduce leisure/social time activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I am bothered by interference (I am disturbed if	62	/	/	Feel bothered by interferences in daily activities

there is noise around me or if I am solicited...).				
I have difficulties in my everyday activities (for example: leisure, social and family life...): I can't multitask as I used to.	63	/	/	Have difficulty multitasking in daily activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I need to check that I haven't made any mistakes.	64	I have difficulties in my everyday and/or professional activities: I need to check that I haven't made any mistakes.	6	Check for errors in daily activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I need more external aids (e.g. diaries, to-do or grocery list, paper notes, monitoring a third party...)	65	/	/	Need external aids for daily activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): Someone needs to tell me what to do and how to do it, because I'm having trouble getting organized	66	/	/	Need instructions in daily activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I need someone to check that I haven't made any mistakes.	67	/	/	Need external checking in daily activities
I have difficulties in my everyday activities (for example: leisure, social and family life...): I had to give up most of my social, domestic, leisure activities.	68	I had to give up part or all of my daily and professional activities.	7	Give up most daily activities
I feel uncomfortable because of the difficulties I encounter, and I tend to withdraw from social situations (for example: I participate less in conversations, I see less my friends, I do less leisure outings...)	69	/	/	Withdraw from social activities
I have balance issues.	70	/	/	Have impaired balance
I cannot walk as long as I used to.	71	/	18	Walk less
I walk slower than before.	72	/	19	Walk slower
I can't go out alone.	73	/	/	Cannot go out alone
I sometimes fall while walking.	74	/	/	Fall while walking
I have difficulty moving my arm(s).	75	/	/	Have difficulty moving arms
I have difficulty moving my leg(s).	76	/	/	Have difficulty moving legs
I have trouble standing for a long time without help.	77	/	/	Have trouble standing
I struggle to pronounce words.	78	/	/	Struggle to pronounce words
Food goes down the wrong way.	79	/	/	Swallow the wrong way
/	/	I feel tired more easily.	20	Feel tired easily

702 **Table S3: Characteristics of participants with CADASIL or another cSVD at inclusion in the**
703 **validation study (significant differences are shown in BOLD).**
704 Legend: The two groups were compared with a T-test when the variable is continuous, a Mann-Whitney U
705 test when the variable is ordinal (modified Rankin Score), and a Chi-square test when the variable is
706 categorical.

	Patients with CADASIL	Patients with other cSVDs	P-value
DEMOGRAPHIC CHARACTERISTICS			
Number of subjects	43	46	
Sex: Male	21 (48.8 %)	24 (52.2 %)	0.918
Laterality: Right-handed	40 (93.0 %)	41 (91.1 %)	1
Education >= High School Diploma	25 (58.1 %)	34 (73.9 %)	0.177
Age at inclusion	56.7 ± 11.8	64.0 ± 13.1	0.00695
Age at Diagnosis (18/ 100)	49.5 ± 11.7	59.0 ± 11.9	<0.001
Time since diagnosis (y) (0/ 100)	7.2 ± 5.9	4.9 ± 5.7	0.0670
TYPE OF RECRUITMENT			
Day hospital	36 (83.7 %)	12 (26.1 %)	
Outpatient consultation	6 (14.0 %)	34 (73.9 %)	
Hospitalization	1 (2.3 %)	0	
CLINICAL MANIFESTATIONS AND SCORES			
Positive stroke history	14 (32.6 %)	23 (51.1 %)	0.180
Ischemic Stroke	14 (32.6 %)	17 (37.0 %)	0.832
Hemorrhagic Stroke	0	7 (15.2 %)	0.0231
modified Rankin score (0/ 6)			0.604
- 0	12 (27.9 %)	17 (37.8 %)	
- 1	16 (37.2 %)	12 (26.7 %)	
- 2	10 (23.3 %)	11 (24.4 %)	
- 3	5 (11.6 %)	5 (11.1 %)	
Apathy Score (0/ 42)	12.4 ± 5.4	13.2 ± 5.9	0.506
VADAS-Cog - SDMT correct answers (0/ 110)	39.3 ± 12.6	30.4 ± 11.3	<0.001
Reactivity index (0/ 100)	91.7 ± 11.9	83.6 ± 19.4	0.0209
Total cued recall (0/ 48)	17.5 ± 6.8	16.9 ± 5.3	0.631
Total free recall (0/ 48)	28.5 ± 7.9	26.3 ± 9.2	0.215
HAD depression (0/ 21)	5.0 ± 4.1	5.8 ± 4.8	0.428
HAD Anxiety (0/21)	7.7 ± 4.3	8.0 ± 4.2	0.666
iADL - current activities (0/ 8)	7.6 ± 1.1	7.7 ± 1.0	0.915
iADL - self care (0/ 6)	5.8 ± 0.6	5.8 ± 0.6	0.924
Working Memory Scale (50/ 150)	99.4 ± 13.2	93.6 ± 18.0	0.991
SSPB - TOTAL (0/ 4)	3.8 ± 0.5	3.6 ± 0.8	0.864
TMT A time (0/ 180)	37.0 ± 19.3	51.0 ± 25.9	0.00498
TMT B errors (0/ 24)	0.4 ± 0.8	1.4 ± 2.2	0.00709
TMT B Time (0/ 300)	84.2 ± 47.4	140.2 ± 81.3	<0.001
Wisconsin - completed categories (0/ 6)	5.7 ± 0.8	4.7 ± 1.7	<0.001
Wisconsin - perseverations (0/ 47)	0.7 ± 1.8	2.8 ± 4.7	0.00850
MRI LESIONS			
Microbleeds	14 (32.6 %)	14 (30.4 %)	1
Transient ischemic attack	4 (9.3 %)	4 (8.7 %)	1
Lacunes	23 (53.5 %)	19 (41.3 %)	0.348
White Matter Lesions	43 (100.0 %)	43 (93.5 %)	0.264
CADA-PRO SCORES			
CADA-PRO total (0/ 72)	30.0 ± 17.2	30.3 ± 16.3	0.666
CADA-PRO Impact on daily activities (0/ 20)	7.1 ± 5.3	7.4 ± 4.6	0.917
CADA-PRO Anxiety-depression (0/ 24)	9.6 ± 6.3	9.9 ± 6.6	0.762
CADA-PRO Attention-EF (0/ 16)	7.4 ± 4.1	6.7 ± 4.0	0.810
CADA-PRO Motor (0/ 12)	5.9 ± 4.1	6.3 ± 4.0	0.419

708
709
710

Table S4: Unrotated factor loadings of the development and validation versions of CADA-PRO.

	Validation study (18-items MIRT)				Development study (19-items FA)			
	F1	F2	F3	F4	F1	F2	F3	F4
1 - Find it difficult to follow a conversation	/	/	/	/	0,66	-0,37	0,18	0,40
2 - Write everything down to remember	/	/	/	/	0,81	-0,32	0,08	-0,13
3 - Find it difficult to do a complex activity	0,65 7	0	0	0	0,79	0,08	-0,16	0,49
4 - Have difficulty deciding	0,69	0	0	0	0,71	0,23	-0,32	0,42
5 - Need more time to complete activities	0,91 5	0	0	0	0,67	-0,47	-0,19	-0,21
6 - Check for errors in daily activities	0,74	0	0	0	0,80	-0,39	-0,15	0,03
7 - Give up most daily activities	0,66 4	0	0	0	0,84	-0,12	-0,32	-0,03
8 - Feel anxious	0	0,959	0	0	-0,42	0,66	-0,24	-0,40
9 - Have ruminations	0	0,932	0	0	-0,34	0,77	0,13	0,26
10 - Lose self-esteem	0	0,962	0	0	-0,06	0,93	-0,13	-0,16
11 - Have pessimistic ideas	0	0,864	0	0	-0,43	0,79	-0,07	0,01
12 - Tend to procrastinate	0	0,794	0	0	-0,20	0,81	0,31	0,04
13 - Lose pleasure or interest	0	0,844	0	0	0,11	0,88	-0,16	0,28
14 - Use one word for another	0	0	0,902	0	-0,21	-0,21	0,67	-0,46
15 - Feel slowed down	0	0	0,926	0	-0,25	-0,01	0,73	-0,18
16 - Look for everyday objects	0	0	0,844	0	0,16	-0,01	0,89	0,07
17 - Go to do something and forget	0	0	0,895	0	-0,23	0,10	0,86	-0,14
18 - Walk less	0	0	0	0,928	0,06	-0,01	-0,20	0,96
19 - Walk slower	0	0	0	0,998	-0,01	0,11	-0,13	0,95
20 - Feel tired easily	0	0	0	0,996	/	/	/	/

711
712

713 **Table S5: Final version of CADA-PRO, with instructions.**

714

715 Legend: CADA-PRO is at present only available in French.

716

717 Nous allons vous poser des questions concernant d'éventuelles difficultés (cognitives,
718 émotionnelles, comportementales ou motrices) qui peuvent apparaître dans certaines affections
719 neurologiques. Lisez attentivement chaque question et **choisissez une réponse selon votre**
720 **état aujourd'hui**. Répondez si, d'après vous, des changements sont apparus par rapport à
721 l'ordinaire.

	Jamais	Rarement <i>moins d'une fois par semaine</i>	Quelquefois <i>environ une fois par semaine</i>	Fréquemment <i>plusieurs fois par semaine mais pas tous les jours</i>	Très souvent <i>pratique- ment tous les jours</i>
1. J'ai des difficultés à effectuer une activité complexe, il peut m'arriver d'oublier une étape et/ou de perdre le fil					
2. J'ai des difficultés à prendre des décisions alors que cela ne me posait pas de problème avant.					
3. J'ai des difficultés dans mes activités de la vie de tous les jours et/ou professionnelles : Il me faut plus de temps pour les accomplir					
4. J'ai des difficultés dans mes activités de la vie de tous les jours et/ou professionnelles : Je dois vérifier que je n'ai pas fait d'erreurs					
5. J'ai dû renoncer en partie ou complètement à la plupart de mes activités quotidiennes et professionnelles					
6. Je me sens anxieux (se), nerveux (se), avec des difficultés à me détendre.					
7. J'ai tendance à ruminer, je suis inquiet (ète).					
8. J'ai perdu confiance en moi.					
9. J'ai des idées pessimistes, je suis découragé(e) par rapport à mon avenir					
10. Je me sens las (se), cela me demande plus d'effort de commencer ce que j'ai à faire et j'ai tendance à remettre au lendemain.					
11. J'ai perdu le plaisir ou l'intérêt pour certaines choses qui d'habitude me plaisent.					
12. J'emploie parfois un mot pour un autre					

13. Je me sens ralenti(e) dans la façon de réfléchir et/ou de faire les choses					
14. Je perds beaucoup de temps à chercher les petits objets du quotidien					
15. Il m'arrive d'entrer dans une pièce pour y faire quelque chose et ne plus savoir quoi					
16. Je ne peux plus marcher aussi longtemps qu'avant					
17. Je marche plus lentement qu'auparavant					
18. Je me sens plus facilement fatigable					

722

723 **Table S6: Internal consistency, test-retest reliability, and proportion of explained variance for the 18**
 724 **items of the final CADA-PRO.**

725
 726 Legend: Internal consistency (N=89) is assessed by Cronbach's alpha, for the total set and for the set
 727 minus the item. Test-retest reliability (N=64) is assessed by Quadratic-weighted Kappas. The proportion of
 728 explained variance by the 4-factor structure (h^2 ; N=89) is given, as well as the factor name for which the
 729 item was constrained to load onto.
 730
 731

Item	Cronbach's α	qw-K*	Factor	h^2
3-Find it difficult to do a complex activity	0.94 (0.92;0.97)	0.66	Daily activities	0.43
4-Have difficulty deciding	0.94 (0.92;0.96)	0.53	Daily activities	0.48
5-Need more time to complete activities	0.94 (0.91;0.96)	0.75	Daily activities	0.84
6-Check for errors in daily activities	0.94 (0.92;0.96)	0.66	Daily activities	0.55
7-Give up most daily activities	0.94 (0.92;0.96)	0.75	Daily activities	0.44
8-Feel anxious	0.94 (0.92;0.96)	0.71	Anx/Dep	0.92
9-Have ruminations	0.94 (0.92;0.96)	0.68	Anx/Dep	0.87
10-Lose self-esteem	0.94 (0.92;0.96)	0.78	Anx/Dep	0.93
11-Have pessimistic ideas	0.94 (0.92;0.96)	0.76	Anx/Dep	0.75
12-Tend to procrastinate	0.94 (0.92;0.96)	0.68	Anx/Dep	0.63
13-Lose pleasure or interest	0.94 (0.91;0.96)	0.79	Anx/Dep	0.71
14-Use one word for another	0.94 (0.92;0.96)	0.53	Attention/EF	0.81
15-Feel slowed down	0.94 (0.91;0.96)	0.68	Attention/EF	0.86
16-Look for everyday objects	0.94 (0.92;0.96)	0.56	Attention/EF	0.71
17-Go to do something and forget	0.94 (0.92;0.96)	0.60	Attention/EF	0.80
18-Walk less	0.94 (0.92;0.96)	0.29	Motor	0.86
19-Walk slower	0.95 (0.92;0.97)	0.78	Motor	0.99
20-Feel tired easily	0.95 (0.92;0.97)	0.60	Motor	0.99

732 *qw-k=quadratic weighted kappa

733

734

735 **Table S7: Multiple regression of CADA-PRO total score on clinical variables that were selected by a**
 736 **stepwise variable selection.**

737
 738 Legend: Predictors were standardized prior to variable selection and regression. We removed predictors
 739 too correlated with others (Pearson correlation >0.7): SAS and TMT A time were dropped, and HAD anxiety
 740 and depression, VADAS-Cog code, Working Memory Index from WMS-III, SSPB-4, FCSRT total free recall
 741 and reactivity index, and the difference between TMT B and A times, were kept. See Figure S4 for the
 742 clinical variables' correlation matrix. During the variable selection process, predictors were added if they
 743 had a T-test p-value >0.1 and increased the model adjusted R-square. They could be removed at the
 744 following steps if they decreased the model adjusted R-square. We selected variables separately to build
 745 two models: one for CADASIL patients only, the other for patients with a different cSVD. The coefficients of
 746 predictors, their 95% CI and p-values obtained for the two models are presented.

747
 748

	CADASIL N=40	Other cSVD N=45
Intercept	31.42 (28.28, 34.56), p<0001	29.32 (26.40, 32.24), p<0001
HAD-anxiety	3.50 (-0.18, 7.17), p=0.062	5.70 (1.99, 9.41), p=0.003
HAD-depression	11.62 (7.53, 15.71), p<0001	8.56 (5.14, 11.99), p<0001
Working Memory Index	-5.36 (-9.23, -1.49), p= 0.008	Not selected

749
 750
 751
 752