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PRECLINICAL BRAIN NETWORK ABNORMALITIES IN PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE

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Running title: Cognition and functional connectivity changes in SCD individuals

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Abstract

Objective: Alzheimer's Disease (AD) is the most common form of dementia worldwide. Currently there are no disease modifying treatments available. Detecting subjects with increased risk to develop dementia is essential for future clinical trials. Subjective cognitive decline (SCD) is a condition defining individuals who perceive a decrease in their own cognitive functioning in the absence of any detectable deficit on neuropsychological testing. SCD individuals show AD-related biomarkers abnormalities in CSF. Aim of the present study was to assess brain functional connectivity (FC) changes in SCD individuals.

Material and Methods: 23 SCD and 33 healthy subjects (HS) underwent an extensive neuropsychological assessment and 3T-MRI scanning including a T1-w volume and resting-state fMRI (RS-fMRI) to assess brain atrophy and brain functional connectivity (FC). Results: no between-group differences in grey matter volumes were detected. SCD subjects compared to HS showed both increased and decreased FC in the executive and parietal networks. Associations between cognitive measures, mainly assessing working memory, and FC within brain networks were found both in SCD and HS separately.

Discussion: SCD individuals showed FC abnormalities in networks involving fronto-parietal areas that may account for their lower visuo-spatial working memory performances. Conclusions: dysfunctions in executive-frontal networks may be responsible for the cognitive decline subjectively experienced by SCD individuals despite the normal scores observed by formal neuropsychological assessment. The present study contributes to consider SCD individuals in an early Alzheimer's disease stage with an increased risk of developing the disease in the long term.

Keywords: Subjective cognitive decline; brain functional connectivity; MRI; cognitive functions

1 **Introduction**

2 Subjective Cognitive Decline (SCD) is a condition defining individuals who perceive a
3 decrease in their own cognitive functioning in the absence of any objective cognitive
4 impairment detectable on standard neuropsychological testing [1]. Over the last decades,
5 there has been growing interest in SCD as an early stage of cognitive decline. This is due
6 to the increased risk of SCD individuals to develop mild cognitive Impairment and to
7 eventually convert to dementia [2, 3]. In 2014, the international SCD-initiative (SCD-I)
8 working group defined a standardised terminology alongside clinical research criteria for
9 the identification of individuals with SCD. Criteria include the following key features: a self-
10 experienced decline in cognitive functioning over time against a previous normal cognitive
11 status, and reporting normal scores on standardised neuropsychological tests adjusted for
12 age, sex and education [1]. A proportion of individuals complaining of SCD who require
13 medical consultation show abnormalities in CSF beta-amyloid and/or tau protein levels [4],
14 which are biomarkers for a neurobiological diagnosis of Alzheimer's Disease (AD).
15 According to the classification proposed by the National Institute on Aging-Alzheimer's
16 Association (NIA-AA), SCD may be regarded as the earliest clinical stage of AD [5]. This
17 classification is based on the consideration that AD pathology begins to develop years
18 before appearance of any significant cognitive decline and that an early detection of the
19 disease is critical for effective treatment and prevention. Against this background,
20 diagnostic criteria for AD have been recently revised to include SCD as a potential early
21 symptom of AD [6].
22 In addition to biomarkers, structural and functional brain alterations have been reported in
23 individuals with SCD. Studies using brain imaging to investigate these alterations have
24 demonstrated that individuals complaining of SCD often show reduced grey matter (GM)
25 volumes in brain regions known to play a key role in memory functions, such as the
26 hippocampus and the parahippocampal gyrus. These structural changes are often

27 accompanied, or preceded, by functional abnormalities in SCD brains [7], with disruption of
28 connectivity in networks associated with memory and cognitive control. Altered (increased
29 or decreased) functional connectivity (FC) was found within the Default Mode Network
30 (DMN) of SCD individuals compared to healthy subjects (HS) [8] or between their DMN
31 and other brain regions such as those belonging to the medial temporal memory system
32 [9] or the hippocampus [10]. Other studies observed FC alterations in the Medial Visual
33 Network [11], Salience Network [12], and changes in Fronto-Parietal Network.

34 Interestingly, the Fronto-Parietal network is implicated in central executive control,
35 cognitive flexibility, and plays a crucial role in cognitive reserve [13].

36 The relationship between SCD and AD pathology is a topic of intense ongoing research in
37 the field of neurodegenerative diseases. Even though SCD cannot be considered yet as a
38 preclinical stage of AD, it represents for a proportion of subjects a unique opportunity for
39 an early diagnosis of AD, with a potential impact on clinical and therapeutic management.
40 Further research is therefore needed to understand the underlying mechanisms of SCD
41 and their relationship with AD pathology.

42 The aim of the present study was to explore, using functional and structural MRI
43 techniques, the relationship between cognitive features and brain abnormalities in SCD
44 individuals. Previous studies have either investigated single networks (8-10,12) or
45 amplitude of low-frequency fluctuations (ALFF) at whole brain level (7,13). In contrast, we
46 aimed here at investigating functional connectivity changes in a plethora of brain networks
47 involved in different aspects of cognition. The idea was to test the hypothesis that SCD
48 individuals may suffer from a subtle but widespread difficulty to use their cognitive system
49 efficiently.

50

51

52 **Methods**

53 **Participants**

54 Twenty-three individuals with SCD were recruited soon after their first visit at the Memory
55 Clinic of IRCCS Santa Lucia Foundation (Rome, Italy). Inclusion criteria for the study
56 included: the presence of subjective memory complaints in daily living; no evidence of
57 cognitive deficits in memory or in other cognitive domains on formal neuropsychological
58 testing; the absence of any other clinical condition that might account for their symptoms.
59 Major medical conditions (e.g., thyroid dysfunction, metabolic disorders, etc) were carefully
60 excluded in all subjects. Similarly, depression, anxiety or major psychiatric disorders were
61 carefully excluded by clinical interview. Thirty-three healthy elderly individuals (healthy
62 subjects; HS) were also recruited by public call on social media. The inclusion criteria for
63 HS were the following ones: no evidence of subjective cognitive complaints in daily living;
64 no evidence of memory or cognitive deficits on formal neuropsychological assessment; no
65 evidence of other neurological conditions, major psychiatric disorders, or major systemic
66 illnesses. All recruited subjects (SCD or HS) with a Hachinski score [14] higher than 4
67 were excluded to reduce the risk of recruiting individuals with cerebrovascular disease.
68 Finally, subjects had to be right-handed as assessed by the Edinburgh Handedness
69 Inventory [15].

70 The principal demographic and clinical characteristics of all participants are summarized in
71 Table 1.

72 The study was approved by the Ethical Committee of Santa Lucia Foundation and written
73 informed consent was obtained from all participants before study initiation. All procedures
74 performed in this study were in accordance with the 1964 Helsinki declaration and its later
75 amendments or comparable ethical standards.

76 **Neuropsychological assessment**

77 All participants underwent an extensive neuropsychological battery including the following
78 tests :Verbal episodic long-term memory: 15-Word List (Immediate and 15-min Delayed

79 recall) [16]; Short Story test (Immediate and 20-min Delayed recall) [17]; Visuo-spatial
80 episodic long-term memory: Complex Rey's Figure (Immediate and 20-min Delayed recall)
81 [17]; Short-term memory: Digit span and the Corsi Block Tapping task forward and
82 backward [18]; Executive functions: Phonological Word Fluency [16] and Modified Card
83 Sorting Test [19] ; Language: Naming objects subtest of the BADA ("Batteria per l'Analisi
84 dei Deficit Afasici". Italian for "Battery for the analysis of aphasic deficits") [20]; Reasoning:
85 Raven's Coloured Progressive Matrices [16]; Constructional praxis: Copy of drawings [16]
86 and Copy of drawings with landmarks [16]; Copy of Complex Rey's Figure [17]. The
87 individual scores reported by SCD individuals and HS subjects on the neuropsychological
88 battery are reported in Supplementary Tables 1A and 1B.

89 For all employed tests, we used the Italian normative data for both score adjustment (sex,
90 age and education) and definition of normal cut-off scores, which were determined as the
91 lower limit of the 95% tolerance interval for a confidence level of 95%. For each test,
92 normative data are reported in the corresponding references.

93 **MRI Acquisition**

94 Brain MRI was performed on a 3T scanner (Magnetom Allegra; Siemens. Erlangen,
95 Germany). The acquisition parameters of each MRI acquisition were as follows: (1) Dual-
96 echo turbo Spin Echo (TSE) (repetition time [TR]=6.190 msec; echo time [TE]=12/109
97 msec); (2) fluid attenuated inversion recovery (FLAIR) (TR=8.170 msec; TE=96 msec.;
98 inversion time [TI]=2.100 msec); (3) T1-weighted 3D MDEFT (TR=1338 ms; TE=2.4 ms;
99 Mmatrix=256x224x17; in-plane FOV=250x250 mm²; slice thickness=1 mm); (4) T2*
100 weighted echo planar imaging (EPI) volumes sensitized to BOLD contrast (TR=2080 ms,
101 TE=30 ms, 32 axial slices parallel to AC-PC line, matrix=64x64, pixel size=3x3 mm², slice
102 thickness=2.5 mm, flip angle:70°). BOLD EPIs were collected during rest for a 7 min and
103 20 s period, resulting in a total of 220 volumes. During this acquisition, subjects were

104 instructed to keep their eyes closed, not to think of anything in particular, and not to fall
105 asleep.

106

107 **Medial temporal lobe atrophy and macroscopic brain tissue abnormalities**

108 The Medial Temporal Lobe Atrophy scale (MTA) [21] was used on T1-weighted images to
109 assess the presence of macroscopic atrophy. For each subject, we averaged the scores
110 obtained from the right and left hemisphere to obtain a single measure of MTA (see Table
111 1). TSE and FLAIR scans were reviewed by an expert radiologist to exclude macroscopic
112 abnormalities. T1-weighted (MDEFT) volumes were all reviewed to exclude macroscopic
113 artefacts before running voxel-based morphometry (VBM) (see below).

114

115 **Image analysis for Voxel-based morphometry**

116 T1-weighted volumes were pre-processed using the optimised voxel based morphometry
117 (VBM) protocol [22-23] implemented in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). This
118 image processing consists of an iterative combination of segmentations and
119 normalisations to produce a GM probability map [22-23] in standard space (Montreal
120 Neurological Institute [MNI] coordinates) for every subject. In order to compensate for
121 compression or expansion which might occur during warping of images to match the
122 template, GM maps were “modulated” by multiplying the intensity of each voxel in the final
123 images by the Jacobian determinant of the transformation, which corresponds to its
124 relative volume before and after warping [23]. GM, white matter (WM) and cerebrospinal
125 fluid (CSF) volumes were computed from these probabilistic images for every subject. All
126 data were then smoothed using a 8-mm FWHM Gaussian kernel.

127

128 **Image Analysis for resting-state functional MRI**

129 The first 4 volumes of each functional MRI (fMRI) time series were discarded to allow for
130 T1 equilibration effects. Then, images were corrected for head motion (using the standard
131 SPM12 realignment algorithm), and compensation for slice-dependent time shifts.
132 Segmentation derived normalization parameters were used to normalize the motion and
133 slice-time corrected EPI images to MNI coordinates. In addition, in order to minimise the risk
134 that our results were affected by differing degree of motion between SCD individuals and HS, we
135 computed the average mean displacement (root mean square or RMS of the 6 realignment
136 parameters) and the average frame-wise displacement (FD) and compared them between groups
137 by using One-way ANOVAs.

138 Independent component analysis (ICA) was employed using GIFT (icatb.sourceforge.net/)
139 to identify 20 independent components. Briefly, GIFT first concatenates the individual data
140 across time, then produces a computation of subject specific components and time
141 courses. The toolbox then performs the following analysis in 3 steps for all subjects
142 grouped together: (1) data reduction, (2) application of the FastICA algorithm, and (3)
143 back-reconstruction for each individual subject. The resulting maps were converted to Z-
144 scores, and components were reviewed to identify the Default Mode Network (DMN), the
145 left and right Fronto-parietal networks (FPNs), the Central Executive Network (CEN) and
146 Salience Network (SN).

147 The goodness of components extracted was tested by using the ICASSO toolbox. We run
148 ICASSO 10 times by using the RandInit mode.

149

150 **Statistical analyses**

151 One-way ANOVA models were used to assess between-group differences (SDC vs. HS) in
152 each neuropsychological score. The accepted p-value was fixed at $p \leq 0.05$.

153 For voxel-based morphometry, statistical analyses of regional GM volumes were
154 performed in SPM-12 using smoothed GM maps within the framework of the general linear

155 model. A two-sample T-test was employed to assess between group differences (SCD
156 and HS) in either direction. Intracranial volumes (obtained by adding up WM volume + GM
157 volume + CSF volume) were entered in all analyses as a covariate of no interest. In VBM
158 imaging analyses results were accepted as significant at $p < 0.05$ FWE corrected values at
159 cluster level.

160

161 Resting-state fMRI second level analyses were performed in SPM12 using a two sample t-
162 test design to compare FC between groups in all considered networks (i.e., DMN; right and
163 left FPN; CEN and SN). Sex entered as nuisance variable in the between-group
164 comparisons.

165 Associations between FC within each network and cognitive scores were also
166 investigated using one-sample t-test models separately for SCD and HS. In resting-state
167 fMRI imaging analyses results were accepted as significant at $p < 0.05$ FWE corrected
168 values at cluster level.

169 **Results**

170 **Demographic and clinical characteristics**

171 As reported in Table 1, there were no significant between-group differences in age
172 ($F_{1,54}=0.04$, $p=0.842$), years of formal education ($F_{1,54}=0.138$, $p=0.712$), MMSE ($F_{1,54}=0.65$,
173 $p=0.420$), and MTA scores ($F_{1,54}=0.029$, $p=0.866$). Sex distribution was different between
174 groups with a higher representation of females in the SCD group (Chi-square=7.1, $df=1$,
175 $p=0.007$).

176 **Neuropsychological assessment**

177 As reported in Table 2, at a group level, SCD individuals reported significantly lower
178 scores than HS in the following neuropsychological tests: Short Story test-20 min Delayed
179 recall ($F_{1,54}=2.871$, $p=0.007$), Corsi Block Tapping backward test ($F_{1,54}= 7.25$, $p=0.009$),
180 Copy of drawings with landmarks ($F_{1,54}= 5.20$, $p=0.026$). As mentioned above, all these

181 scores were used to assess possible associations with measures of FC (covariates of
182 interest) in each group separately.

183 **Voxel-based morphometry**

184 There were no significant differences in regional GM volumes between SCD individuals
185 and HS.

186

187 **Resting-state fMRI**

188 There were no significant differences between groups in the mean motion parameters
189 RMS (SCD=0.67, HS=0.57, $F_1=1.77$, $p=0.188$) and in the mean FD (SCD=0.56, HS=0.58,
190 $F_1=0.03$, $p=0.860$).

191 As summarized in the Supplementary Figure the ICA components showed a good
192 convergence and stable decomposition indicating a high reliability of the brain networks
193 extracted mainly of those included in the analyses.

194 **Cross-sectional analysis**

195 We observed significant FC differences between SCD individuals and HS in some but not
196 all considered brain networks in either direction. As shown in Figure 1 and Table 3, when
197 considering the FPN, SCD individuals compared to HS showed a significant decreased FC
198 in the right hippocampus, in the right parahippocampal gyrus and in the cerebellum.
199 Conversely, SCD individuals showed increase of FC mainly involving the left angular
200 gyrus. When considering the CEN, SCD subjects compared to HS showed reduced FC in
201 the right posterior cingulate cortex and precuneus.

202

203 **Associations between functional brain connectivity and cognitive measures**

204 In the SCD group, we observed a negative association between Corsi Block Tapping test
205 scores and FC in the right cingulate gyrus within the CEN (see Table 5 and figure 6).

206 In HS, as shown in Table 4 and figure 3, we observed a significant positive association
207 between Corsi block tapping test scores and FC in the right supplementary motor cortex
208 and the left cingulate gyrus within the FPN. Additionally, in the HS group, positive and
209 negative associations were found between Corsi block tapping test scores and FC within
210 the CEN. A positive association was found in the left middle temporal gyrus, putamen and
211 thalamus, while a negative association was found in the right fornix and in the left
212 parahippocampal gyrus. Finally, as shown in Figure 5, we observed in HS a positive
213 association between Copy of drawings with landmarks test scores and FC in the left
214 cingulate gyrus within the CEN.

215

216 **Discussion**

217 The present study aimed at investigating potential associations between cognitive
218 measures and structural and functional brain alterations in individuals with SCD.
219 We compared individuals with SCD to HS and we did not find any significant differences
220 between the two groups in age, education level, MMSE, and MTA scores. However, a
221 significant difference was observed in sex distribution, with a higher proportion of females
222 in the SCD group. This finding is in line with previous studies showing a higher prevalence
223 of AD and cognitive impairment in women compared to men [24, 25]. It has been
224 suggested that sex differences in AD may be attributed to hormonal, genetic, and lifestyle
225 factors [26]. The higher prevalence of SCD in women was previously explained as due to a
226 higher prevalence of anxiety and depression in this group [27]. Although we did not
227 perform a formal comparison between females and males nobody individual showed
228 abnormal levels of depression and anxiety at clinical interview. However, these results
229 highlighted the importance of considering sex differences in both research and clinical
230 practice related to AD and cognitive decline since early stage.

231 Despite a performance within the cut-off ranges of normality in all administered
232 neuropsychological tests, SCD individuals as a group performed worse than HS in some
233 domains, such as episodic verbal memory (i.e., Short Story Test). Previous studies in AD
234 have identified early deficits in patient retrieval of learned information from story recall
235 tasks as compared to free recall of word lists [28]. This dissociation suggests the existence
236 of distinct cognitive and neural mechanisms underlying the recall of stories and word lists
237 [29]. A word list test requires an active effort to organize semantically unrelated material
238 during both encoding and retrieval [28]. On the contrary, in a story recall task, the material
239 is already well organized from a semantic and logical perspective, thus requiring passive
240 learning and less demanding retrieval strategies [28]. This idea is supported by evidence
241 that patients with frontotemporal dementia perform better than those with AD on the Story
242 test, due to the advantage given by semantic facilitation. Conversely, AD patients who do
243 not benefit from any semantic facilitation perform poorly also at the Story test. In our
244 hypothesis, SCD individuals who performed worse (as a group) than HS in the Story test,
245 might reflect a very early impairment in benefiting from semantic facilitation when required
246 to organise organization their memoranda. In addition, SCD individuals reported poorer
247 scores than HS in the Copy of drawings with landmark test. This is a constructional praxis
248 task in which elements of different shapes (i.e., star, cube and house) are presented on a
249 sheet on which subjects are required to connect them and obtain the correct shapes. This
250 task is more demanding in terms of planning strategies compared to a free copy of
251 drawings task, requiring the ability to organize fragmented elements into a globally
252 corrected shape. This task is typically impaired in AD patients with remarkable executive
253 deficits since early disease stages. Finally, our SCD individuals reported lower scores than
254 HS in the backward Corsi blocking Tapping task, which measures visuo-spatial working
255 memory. Previous research reported deficits in working memory in individuals with SCD
256 [30], which may be related to dysfunction in their prefrontal cortex and the hippocampus

257 [31]. These findings suggest that working memory deficits may be an early marker of
258 cognitive decline, and a potential target for early intervention in SCD. Taken together all
259 these results indicate an early difficulty of SCD individuals in engaging their executive
260 functions. In our hypothesis, SCD individuals do not suffer from a specific pattern of
261 cognitive impairment, but rather show a general difficulty to access their executive system.
262 This may indeed be responsible itself for the cognitive deficits that SCD individuals
263 subjectively experience. Executive dysfunctions have been previously described in SCD
264 populations [32-34]. Impairment of higher executive abilities, such as the divided attention
265 or flexibility, may impact on free recall during memory tasks [33, 35].
266 In the present study we did not find any brain volumetric changes in SCD individuals
267 compared to HS. In the literature there have been reported controversial results on this
268 subject. Some studies reported decreased hippocampal volume in SCD subjects [36, 37,
269 38, 39, 40], while other studies failed in identifying any significant hippocampal atrophy
270 [41, 42, 43, 44, 45]. This might be explained by a high heterogeneity of SCD individuals,
271 whose mismatch between regional brain volumetrics and symptoms may be accounted in
272 either direction by other factors, such as cognitive reserve [46].
273 Conversely, in the current study we identified significant differences between SCD
274 individuals and HS in functional brain connectivity within the FPN and CEN, which are
275 regard as networks critically involved in cognition [47-48]. When looking at the FPN,
276 individuals with SCD showed FC changes in either direction within the right hippocampus
277 and the parahippocampal gyrus bilaterally, and increases in left angular gyrus. These
278 findings are consistent with the well-known notion that the hippocampus and medio-
279 temporal cortices are involved in the encoding, storage and retrieval of long-term memory
280 traces [49]. In addition, the left angular gyrus has been previously associated with higher
281 level functions, including memory and awareness [50]. We might argue that the decrease
282 of FC in the hippocampus and its increase in the angular gyrus might account for the

283 memory difficulties that are subjectively experienced by SCD individuals. Additionally,
284 reduced FC of the hippocampus might explain why SCD individuals retrieve items
285 incorrectly, while increased FC of the angular gyrus might be interpreted as a
286 compensatory mechanism against hippocampal failure in driving memory performance into
287 the normal range. Finally, increased FC of the angular gyrus might explain why individuals
288 with SCD are subjectively aware of their own cognitive difficulties.

289 When considering the CEN, SCD individuals showed lower connectivity mainly in the right
290 posterior cingulate cortex and in the precuneus. These areas are involved in memory and
291 cognitive functions [51, 52] and have been found disrupted in AD since its early clinical
292 stages [53, 54]. In support to this view, we found also a negative association between
293 SCD subjects' performance on visuo-spatial working memory tests and FC of the posterior
294 cingulate cortex. Interestingly, in the AD continuum, the precuneus has been identified as
295 a critical structure of the DMN, whose disconnection precedes local atrophy [55], is
296 modulated by reserve mechanisms [55, 56] and may be contrasted by non-
297 pharmacological interventions [52].

298 When looking at the FPN in HS in isolation, we found a positive association between their
299 Corsi span blocking test scores and FC in the supplementary motor cortex and in the left
300 cingulate gyrus. This finding is in line with the observation that several motor regions,
301 including the supplementary motor area, are simultaneously engaged in working memory
302 tasks [57-58]. Unfortunately, the Corsi span blocking test does not allow us to disentangle
303 between different modules involved in the working memory function. According with
304 Baddley [59, 60], working memory functions involve the central executive system, the
305 phonological loop and the visuospatial sketchpad. We can only hypothesise that the CEN
306 may differently control the central executive system and the visuospatial sketchpad, thus
307 contributing to their normal functioning in healthy subjects. Finally, HS showed a positive
308 association between performance at the Copy of drawings with landmarks task and FC of

309 the Cingulate gyrus, within the CEN. The cingulum has been previously found to be
310 involved in the correct execution of constructional praxis tasks [61]. Deficits in constructive
311 praxis are regarded as a hallmark of AD, and have been linked to dysfunction in the
312 posterior parietal and in the prefrontal cortex [61]. Interestingly, the cingulum plays a
313 critical role in connecting each other these different parts of the brain.

314 Our imaging findings went in either direction, an increase or a decrease of functional
315 connectivity within networks. A classical neurobiological interpretation of decreases and
316 increases of connectivity are network disruption in the former case and compensatory
317 mechanisms of brain plasticity in the latter case [62-64]. Main contribution to this
318 interpretation comes from longitudinal studies, which documented an increase of
319 functional connectivity passing from mild cognitive impairment status to dementia [65-67].
320 One of the limitations of the present study is the absence of any neurobiological markers
321 (e.g., CSF; PET imaging) for the diagnosis of AD in our cohort. Nonetheless, cognitive
322 profile and brain connectivity were significantly different between SCD subjects and
323 controls, reinforcing the idea that former group diverts from a “healthy pathway”. Another
324 limitation of this study is the relatively small sample-size, which requires future
325 confirmatory studies on larger populations. Partially related to this point, there a mismatch
326 between males and females in the two groups, due to consecutive recruitment of patients.
327 Despite out of the scope of the present study, such a mismatch would also deserve to be
328 further investigated itself in the framework of gender differences in response to the same
329 pathological condition. However, our sample size does not allow such an additional
330 analysis. Future studies on larger populations are needed.

331 In conclusion, the present study contributes in considering SCD as a high risk condition
332 for developing AD over time. Biomarkers of AD pathology, as well as alterations in brain
333 structure and function, have been previously described in SCD individuals, with

334 remarkable implications for an early detection and treatment of AD. Brain connectivity,
335 appears as a potential sensitive tool for patient stratification and clinical trial monitoring.

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341 **Conflict of interest**

342 The authors have no conflict of interest to report.

343 **Data Availability" statement**

344 All data are available contacting the Santa Lucia Foundation IRCCS

345

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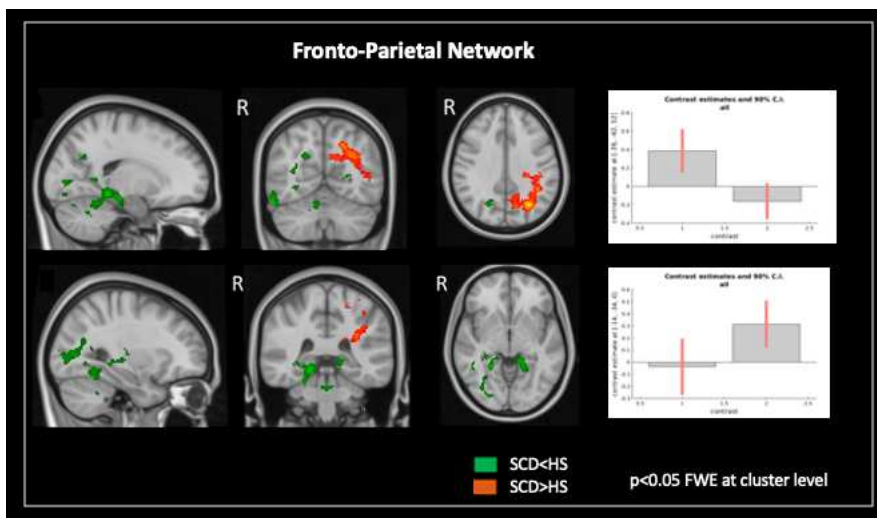
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Figures

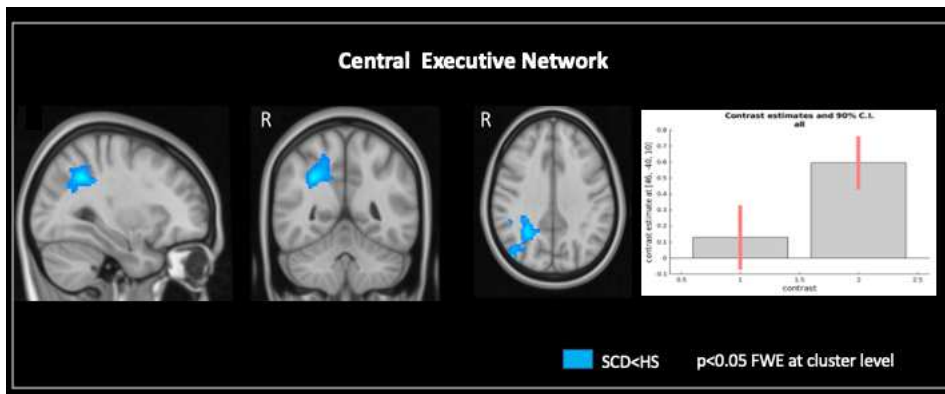
Figure 1.



The figure illustrates both increase (in red, in the parietal regions) and decrease (in green, in the hippocampus and parahippocampus) of functional connectivity within the Fronto-Parietal Network in Subjective Cognitive Decline individuals compared to healthy subjects. The scatterplots show the between-group differences in functional connectivity in the peak clusters. The results are overlaid onto the Ch2 template of MRICron in MNI coordinates. See text for further details.

Abbreviations: HS= Healthy Subjects; FWE=Family Wise Error; R= Right; SCD=Subjective Cognitive Decline.

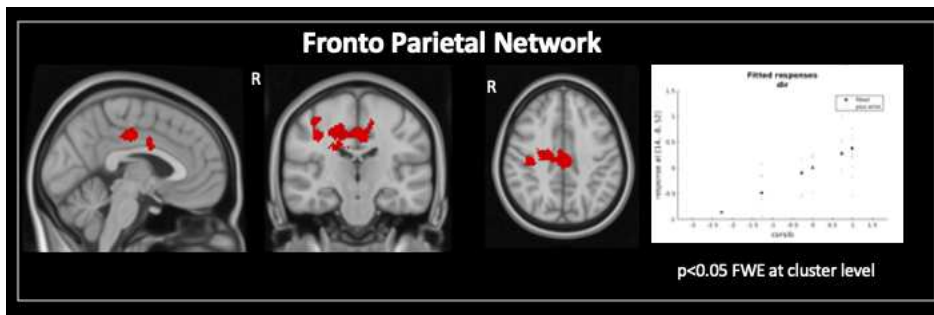
Figure 2.



The figure shows the decreased functional connectivity in the parietal regions within the Central Executive Network in Subjective Cognitive Decline individuals compared to healthy subjects. The scatterplot shows the between-group differences in functional connectivity in the peak clusters. The results are overlaid onto the Ch2 template of MRICron in MNI coordinates. See text for further details.

Abbreviations: HS= Healthy Subjects; FWE=Family Wise Error; R= Right; SCD=Subjective Cognitive Decline.

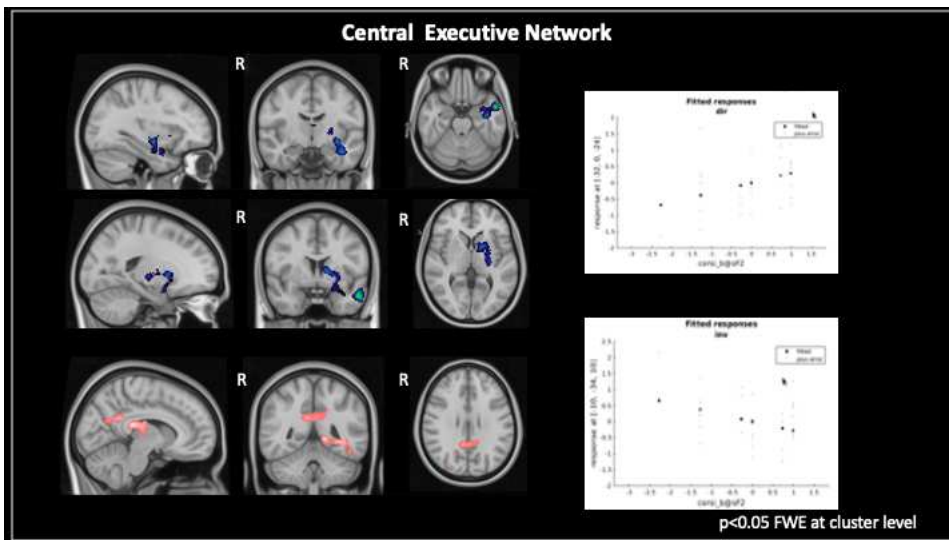
Figure 3.



In this figure is reported the result of the association between the performance obtained by healthy subjects at the Corsi Block Tapping test and functional connectivity in the posterior cingulate cortex within the Fronto-Parietal Network. The scatterplot shows the direct association between the test's scores and the functional connectivity in the peak cluster at individual level. The results are overlaid onto the Ch2 template of MRICron in MNI coordinates. See text for further details.

Abbreviations: FWE=Family Wise Error; R= Right.

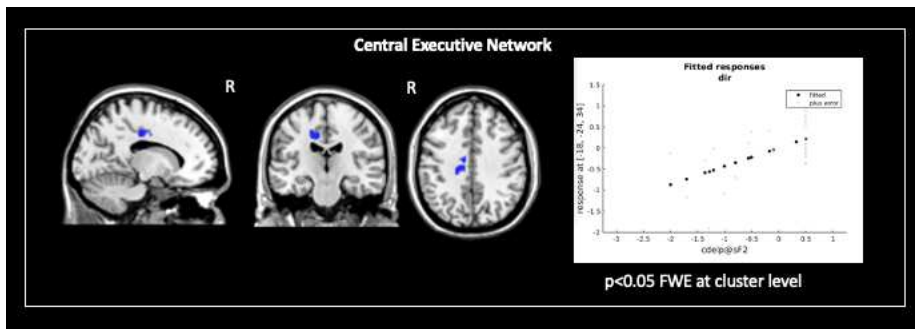
Figure 4.



The figure reports associations between the performance obtained by healthy subjects at the Corsi Block Tapping test and functional connectivity in the several areas within the Central Executive Network. The scatterplots show direct and inverse associations between the test's scores and the functional connectivity in the peak clusters at individual level. The results are overlaid onto the Ch2 template of MRICron in MNI coordinates. See text for further details.

Abbreviations: FWE=Family Wise Error; R= Right.

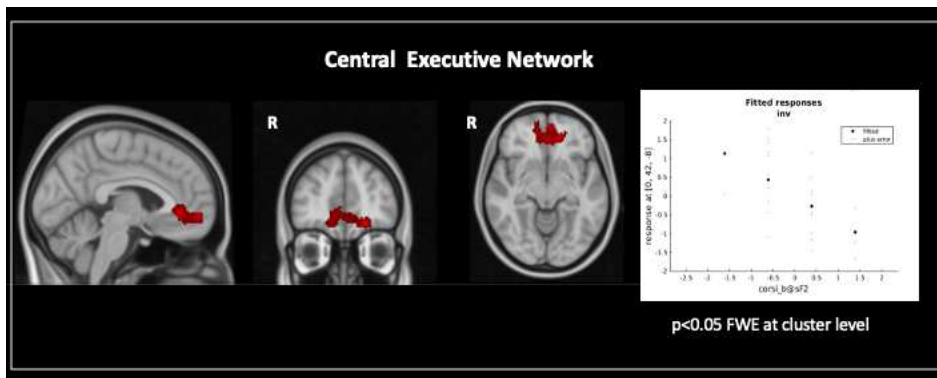
Figure 5.



The figure reports association between the performance obtained by healthy subjects at the Copy of drawings test and functional connectivity in the posterior cingulate gyrus within the Central Executive Network. The scatterplot shows the direct associations between the test's scores and the functional connectivity in the peak clusters at individual level. The results are overlaid onto the Ch2 template of MRICron in MNI coordinates. See text for further details.

Abbreviations: FWE=Family Wise Error; R= Right.

Figure 6.



The figure reports associations between the performance obtained by individuals with Subjective Cognitive Decline at the Corsi Block Tapping test and functional connectivity in the anterior cingulate cortex within the Central Executive Network. The scatterplot shows the inverse associations between the test's scores and the functional connectivity in the peak clusters at individual level. The results are overlaid onto the Ch2 template of MRICron in MNI coordinates. See text for further details.

Abbreviations: FWE=Family Wise Error; R= Right.

Supplementary Figure 1

The panel illustrates the results derived by ICASSO analysis on resting-state fMRI data.

See text for further details

Table 1. Demographic and clinical characteristics of studied subjects

	SCD	HS
	(N=23)	(N=33)
Age (mean± SD)	65.8± 8.4	65.4 ± 8.0
Sex M/F	5/18*	19/14
Years of formal education (mean± SD)	13.5± 3.8	13.2± 3.2
MMSE score (mean± SD)	28.6± 1.9	29.0± 1.0
MTA score (mean± SD)	0.71± 0.7	0.75±0.6

*p-level ≤ 0.05

Abbreviations: HS=Healthy Elderly; MMSE= Mini Mental State Examination; MTA= Medial Temporal Lobe Atrophy; SCD= Subjective Cognitive Disorder.

Table 2 Neuropsychological results

	SCD	HS	p-value
Verbal Episodic			
long-term			
memory			
15-Word List	43.6 (7.5)	45.9 (9.1)	0.302
IR mean (SD)			
15-Word List	9.0 (2.4)	9.7 (2.2)	0.302
15-min DR			
mean (SD)			
15-Word list	13.2 (1.8)	13.9 (0.9)	0.059
Recognition hit-			
rates mean			
(SD)			
15-Word list	1.1 (1.6)	1.4 (1.2)	0.471
Recognition			
false mean			
(SD)			
Short Story	5.6 (1.1)	6.1 (1.1)	0.096
Immediate			
recall mean			
(SD)			

	Short Story 20-	5.3 (1.1)	6.1 (0.9)	0.007
	mim Delayed			
	recall mean			
	(SD)			
<hr/>				
Visuo-spatial				
Episodic long-				
term memory				
	Rey's Complex	16.4 (5.2)	15.8 (5.7)	0.712
	Figure IR mean			
	(SD)			
	Rey's Complex	16.9 (4.8)	15.2 (5.0)	0.206
	Figure 20-min			
	DR mean (SD)			
<hr/>				
Verbal Short-				
term and				
Working				
Memory				
	Digit Span	5.7 (0.8)	5.9 (1.0)	0.577
	forward mean			
	(SD)			
	Digit Span	4.4 (0.8)	4.5 (0.7)	0.702
	backward mean			
	(SD)			
<hr/>				
Visuo-spatial				
Short-term and				

Working				
Memory				
	Corsi Block	5.0 (0.6)	5.0 (0.8)	0.989
	Tapping			
	forward mean			
	(SD)			
	Corsi Block	4.6 (0.8)	5.3 (0.9)	0.009
	Tapping			
	backward mean			
	(SD)			

Executive				
functions				
	Phonological	34.3 (10.6)	36.7 (9.1)	0.364
	verbal fluency			
	Mean (SD)			
	Modified Card	5.8 (0.6)	5.9 (0.3)	0.402
	Sorting test			
	Criteria			
	achieved mean			
	(SD)			
	Modified Card	1.3 (1.8)	1.3 (1.9)	0.928
	Sorting test			
	Perseverative			
	errors mean			
	(SD)			

Language				
	Naming mean (SD)	29.2 (1.8)	29.1 (0.8)	0.732
Logical Reasoning				
	Raven's Coloured Matrices mean (SD)	30.7 (4.0)	32.4 (2.9)	0.078
Constructional Praxis				
	Copy of drawings mean (SD)	11.0 (0.9)	11.0 (1.2)	0.560
	Copy of drawings with Landmarks mean (SD)	68.9 (0.9)	69.5 (0.8)	0.026
	Rey's Complex Figure Copy Mean (SD)	32.7 (2.8)	32.7 (2.3)	0.901

Table 3. Functional connectivity into brain networks between groups

Brain network	Contrast	Brain regions	Side	Size	Z-score	MNI coordinates (mm)		
						x	y	z
FPN								
	<i>SCD<HE</i>	Parahippocampal gyrus	L	3640	3.09	-18	-24	-18
		Hippocampus	R		2.51	22	-37	6
		Parahippocampal gyrus	R		1.28	22	-50	4
	<i>SCD>HE</i>	Occipital cortex	L	1980	2.42	-28	-66	34
		Angular gyrus	L		2.00	-38	-42	50
		Supramarginal gyrus	L		2.04	-42	-50	18
CEN	<i>SCD<HE</i>	Angular Gyrus	R	1650	3.28	30	-50	48
		Angular Gyrus/lateral occipital cortex	R			40	-63	44
		Precuneus	R			8	-58	50

Table 4. Functional connectivity into brain networks and associations with cognitive measures in Healthy subjects.

Brain network	Cognitive tests	association	Brain regions	Side	Size	Z-score	MNI coordinates (mm)		
							x	y	z
FPN	<i>Corsi block tapping test</i>	Positive	Supplementary motor cortex	R	2016	4.30	14	-8	52
			Cingulate gyrus	L		3.39	-6	-22	38
CEN	<i>Corsi block tapping test</i>	Positive	Middle temporal l gyrus	L	1795	3.97	-54	2	-26
			Putamen	L		3.28	-32	-10	-10
		Thalamus	L			-12	0	8	
		Negative	Fornix	R	1936	3.84	8	-30	16
			Parahippocampal gyrus	L		3.12	-14	-48	0

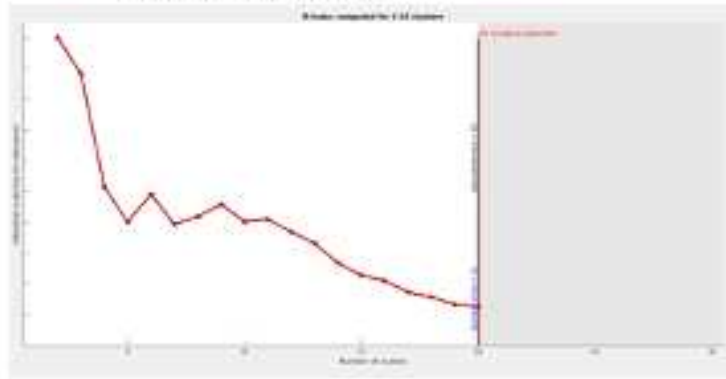
Copy of	Positive	Cingulat	L	176	4.53	-16	-22	42
Drawings		e gyrus						
with								
landmarks								

Table 5. Functional connectivity into brain networks and associations with cognitive measures in Subjective Cognitive Decline individuals.

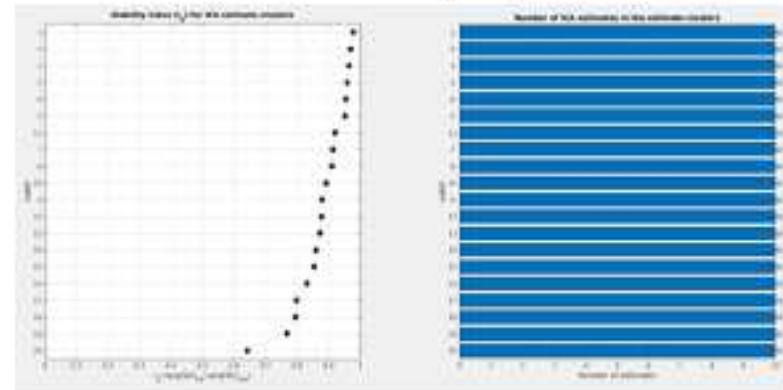
Brain network	Cognitive tests	association	Brain regions	Side	Size	Z-score	MNI coordinates (mm)		
							x	y	z
CEN	<i>Corsi block tapping test</i>	Negative	Cingulate gyrus	R	1638	3.52	2	40	-4

Supplementary Figure 1.

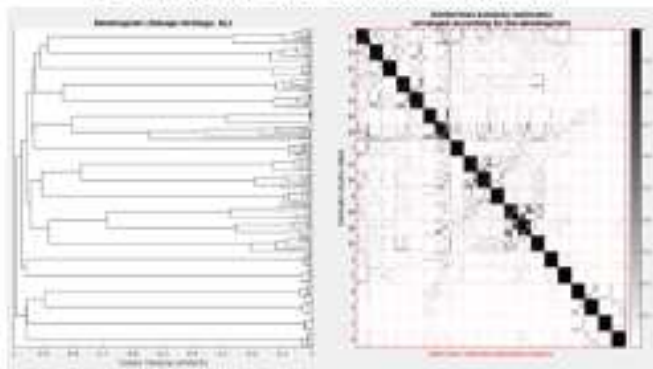
Clustering quality



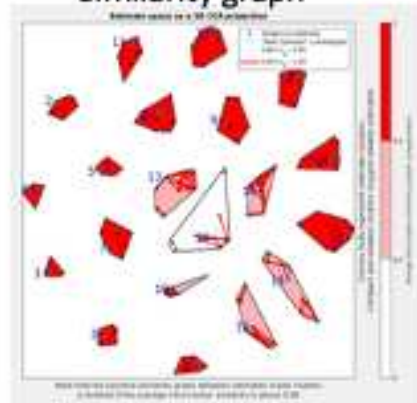
Estimate quality



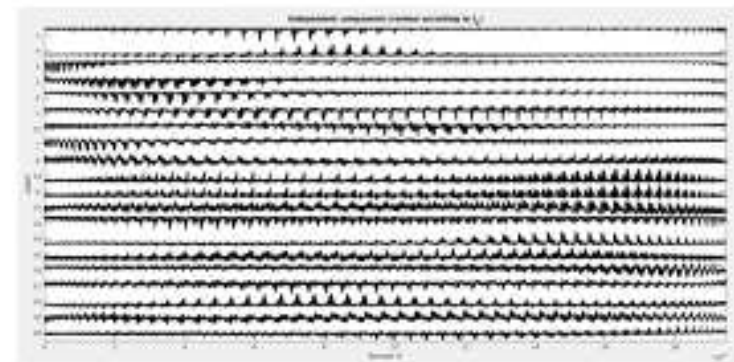
Dendrogram and Similarity matrix



Similarity graph



Source Estimate



Supplementary Table 1A.

	SCD 1	SCD 2	SCD 3	SCD 4	SCD 5	SCD 6	SCD 7	SCD 8	SCD 9	SCD 10	SCD 11	SCD 12	SCD 13	SCD 14	SCD 15	SCD 16	SCD 17	SCD 18	SCD 19	SCD 20	SCD 21	SCD 22	SCD 23
MMSE	30.0	30.0	30.0	25.2	30.0	30.0	30.0	26.0	30.0	26.4	27.3	30.0	27.7	26.2	30.0	30.0	25.7	25.2	30.0	30.0	30.0	30.0	30.0
V-LTM																							
<i>15WL-IR</i>	37.3	41.6	37.3	40.7	42.3	60.6	49.5	43.2	54.7	40.9	40.7	43.2	51.1	32.9	48.5	38.5	40.3	28.8	36.8	40.9	48.3	54.6	50.8
<i>15WL_DR</i>	6.4	6.8	6.5	8.7	7.9	15.0	13.1	9.0	12.7	8.6	7.5	9.0	9.1	7.5	11.0	5.1	8.7	6.1	8.3	10.9	9.8	9.0	10.6
<i>15WLi-HR</i>	10.0	14.0	15.0	13.0	14.0	14.0	15.0	11.0	15.0	13.0	10.0	15.0	15.0	11.0	14.0	13.0	13.0	9.0	14.0	15.0	12.0	14.0	15.0
<i>15WL-FA</i>	2.0	0.0	1.0	1.0	1.0	0.0	0.0	6.0	0.0	2.0	0.0	0.0	2.0	1.0	0.0	4.0	0.0	0.0	4.0	0.0	1.0	0.0	1.0
<i>SS-IR</i>	5.7	6.7	6.5	6.7	6.7	5.7	6.9	8.0	6.0	5.7	7.3	5.5	5.7	6.4	5.7	4.7	3.4	4.8	3.8	5.7	5.7	4.7	5.3
<i>SS-DR</i>	5.6	6.4	6.2	6.5	6.5	5.3	6.6	8.0	5.9	5.3	3.9	5.1	5.3	6.4	5.2	4.2	3.8	4.8	3.5	5.3	5.2	4.6	5.1
VS-LTM																							
<i>CRF-IR</i>	10.8	10.9	24.3	10.5	18.0	23.3	20.4	14.1	28.6	20.1	16.1	13.3	25.6	13.6	12.1	13.8	17.4	9.4	14.7	16.4	11.1	15.5	16.8
<i>CRF-DR</i>	11.9	9.7	23.3	13.6	19.4	23.9	18.3	14.4	28.6	18.7	16.1	14.6	25.8	14.6	15.6	13.9	16.6	9.4	17.2	16.9	13.2	16.1	17.2
V-STM and V-WM																							
<i>DS-F</i>	4.1	6.4	5.5	6.5	5.6	4.8	6.3	5.8	6.5	4.3	4.0	7.3	5.8	6.5	5.8	5.2	5.8	4.5	6.2	6.3	5.5	5.8	5.5
<i>DS-B</i>	6.0	6.0	5.0	5.0	5.0	4.0	5.0	4.0	5.0	3.0	6.0	5.0	4.0	4.0	4.0	4.0	3.0	5.0	4.0	3.0	4.0	5.0	5.0
VS-STM and VS-WM																							
<i>CBT-F</i>	5.0	4.7	4.1	5.9	6.0	5.3	5.7	5.4	5.1	5.5	6.0	4.7	5.8	4.1	3.8	4.7	5.5	5.1	4.9	5.5	4.8	4.0	4.8
<i>CBT-B</i>	4.0	4.0	5.0	6.0	5.0	4.0	5.0	5.0	4.0	4.0	6.0	4.0	4.0	4.0	4.0	5.0	3.0	6.0	5.0	5.0	5.0	5.0	4.0
EXE-F																							
<i>PVF</i>	57.3	28.5	55.9	53.1	24.2	25.3	31.8	20.3	42.1	40.7	31.2	38.7	26.4	29.8	22.3	41.8	29.9	37.5	19.9	35.9	31.5	29.3	35.2
<i>MCST-CA</i>	6.0	6.0	6.0	6.0	6.0	6.0	6.0	5.0	6.0	5.0	5.8	6.0	5.0	6.0	6.0	6.0	6.0	6.0	6.0	5.8	6.0	6.0	6.0

<i>MCST-PE</i>	3.0	0.0	0.0	0.0	0.0	1.0	0.0	4.0	0.0	5.0	1.3	0.0	6.0	0.0	0.0	1.0	4.0	0.0	1.0	1.3	1.0	0.0	1.0	
Lang																								
<i>Naming</i>	30.0	30.0	29.0	30.0	30.0	30.0	30.0	27.0	30.0	28.0	30.0	30.0	29.0	30.0	30.0	30.0	28.0	30.0	30.0	30.0	22.0	29.0	30.0	
LR																								
<i>RPCM</i>	20.1	29.4	35.4	32.6	33.7	26.8	31.7	32.7	34.6	29.3	29.1	31.6	29.2	24.3	30.8	26.8	27.4	31.9	28.9	36.0	32.4	36.0	36.0	
CP																								
<i>CD</i>	11.6	9.0	11.8	10.8	11.6	11.8	10.0	9.9	11.8	11.8	12.0	10.0	11.8	10.7	10.4	11.3	11.8	11.9	10.3	9.6	10.4	12.0	12.0	
<i>CDWL</i>	67.7	67.6	69.7	69.8	69.4	69.4	67.7	69.5	69.8	69.4	70.0	67.6	69.4	67.7	68.1	68.1	68.4	69.9	68.1	68.0	70.0	70.0	70.0	
<i>CRF-C-</i>	29.9	31.9	36.0	32.2	35.6	36.0	33.1	29.4	34.2	33.0	35.8	32.1	30.4	34.0	31.3	29.9	34.2	34.5	25.0	32.8	36.0	36.0	30.0	

Abbreviations: 15-WL-IR= 15-Word List-Immediate Recall; 15-WL-DR= 15-Word List-Delayed Recall; 15-WL-HR= 15-Word List-Hit Rates; 15-WL-FA= 15-Word List-False Alarms; CRF-C= Complex Rey's Figure-Copy; CRF-IR= Complex Rey's Figure-Immediate Recall; CRF-DR= Complex Rey's Figure-Delayed Recall; CBT-F= Corsi Block Tapping test Forward; CBT-B= Corsi Block Tapping test Backward; CD= Copy of drawings; CDWL= Copy of Drawing With Landmarks; CP= Constructional Praxis; DS-F= Digit span Forward; DS-B= Digit span Backward; EXE-F= Executive functions; Lang= Language; LR= Logical Reasoning; MMSE=Mini Mental State Examination; MCST-CA= Modified Card Sorting Test-Criteria Achieved; MCST-PE= Modified Card Sorting Test-Perseverative Errors; PVF= Phonological Verbal Fluency; RPCM= Raven's Progressive Coloured Matrices; SS-IR= Short Story- Immediate Recall; SS-DR= Short Story- Delayed Recall; V-LTM= Verbal Long-Term Memory; VS-LTM=Visuo-spatial Long-Term memory; V-STM= Verbal Short-Term Memory; V-WM= Verbal-Working Memory; VS-STM= Visuospatial-Short-Term Memory; VS-WM= Visuospatial-Working Memory.

Cut-offs: 15-WL-IR cut-off>28.5; 15-WL-DR cut-off>4.6; CD cut-off>7.1; CDWL cut-off >61.8; CRF-C cut-off >23.7; CRF-IR cut-off>6.4; CRF-DR cut-off>6.3; CBT-F cut-off>3.5; CBT-B cut-off>3.0; DS-F cut-off>3.7; DS-B cut-off>2.6; MCST-CA cut-off>4.2; MCST-PE cut-off>7.6; MMSE cut-off >23.7; Naming cut-off>22; PVF cut-off>17.1; RPCM cut-off>18.9; SS-IR cut-off>3.1; SS-DR cut-off>2.8.

See text for further details

Supplementary Table 1B

	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
MMSE	30.0	30.0	26.2	30.0	30.0	30.0	29.3	29.7	28.5	30.0	25.1	29.3	25.0	30.0	30.0	30.0	29.3	30.0	30.0	30.0	26.5	29.3	30.0
V-LTM																							
15WL-IR	57.5	48.8	38.0	37.7	56.0	37.9	56.0	58.0	43.6	51.9	40.4	56.0	46.7	60.2	51.8	35.0	56.0	36.6	50.4	48.8	29.6	56.0	40.3
15WL-DR	12.1	10.1	5.8	9.1	14.6	5.8	10.0	11.0	11.0	11.1	7.6	10.0	8.0	15.0	9.6	8.3	10.0	6.8	8.2	11.6	9.0	10.0	11.4
15WL-HR	14.0	15.0	15.0	13.0	14.0	13.0	14.0	15.0	14.0	15.0	12.0	14.0	14.0	15.0	15.0	14.0	14.0	14.0	15.0	15.0	11.0	14.0	15.0
15WL-FA	0.0	1.0	4.0	3.0	1.4	1.0	1.0	0.0	0.0	0.0	3.0	1.4	0.0	0.0	3.0	1.4	1.4	1.4	1.0	0.0	1.0	1.4	5.0
SS-IR	8.0	5.5	7.1	8.0	6.2	4.3	6.2	6.4	8.0	3.7	7.1	6.2	4.6	7.6	7.4	6.4	6.2	6.2	5.4	6.4	4.0	6.2	6.7
SS-DR	7.8	5.5	6.9	5.7	6.1	5.2	6.1	6.0	8.0	4.6	7.4	6.1	4.6	7.2	6.3	6.1	6.1	6.1	5.6	6.2	3.9	6.1	6.6
VS-LTM																							
CRF- IR	12.4	7.3	28.2	10.3	15.8	13.2	15.8	16.0	17.7	25.4	17.1	15.8	10.5	22.3	20.3	24.0	15.8	15.8	13.1	9.6	22.2	15.8	15.2
CRF-DR	13.9	7.4	25.4	6.4	15.2	8.2	15.2	15.0	19.1	25.0	15.9	15.2	12.0	19.6	21.2	18.0	10.2	16.9	13.6	12.2	26.1	15.2	15.4
V-STM and V-WM																							
DS-F	7.2	4.5	5.5	4.5	8.0	4.6	6.5	6.0	5.8	7.6	6.4	6.5	5.7	5.5	5.5	6.4	6.5	5.4	6.3	5.5	5.8	6.5	5.5
DS-B	4.0	4.0	5.0	4.0	3.0	4.0	5.0	5.0	4.0	5.0	4.0	5.0	4.0	4.0	6.0	6.0	5.0	4.5	4.0	4.8	4.0	5.0	4.0
VS-STM and VS-WM																							
CBT-F	5.9	4.0	5.9	5.0	5.3	5.0	5.3	5.0	4.0	5.0	4.2	5.3	6.0	5.8	5.0	6.0	5.3	5.3	4.4	6.0	4.0	5.3	3.8
CBT-B	6.3	4.0	6.0	6.3	6.3	6.0	6.3	5.0	5.0	6.3	5.0	6.3	6.0	4.0	6.3	6.3	6.3	6.0	4.0	6.0	4.0	5.3	4.0
EXE-F																							
PVF	33.8	32.5	54.2	44.8	35.0	32.1	38.9	39.9	33.3	31.4	36.5	39.9	25.4	24.6	35.2	46.1	38.9	39.5	44.3	52.2	21.3	38.9	30.3

MCST-CA	6.0	6.0	6.0	6.0	5.9	5.0	6.0	5.9	6.0	6.0	6.0	5.9	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
MCST-PE	0.0	0.0	0.0	4.0	1.0	2.0	1.0	1.0	0.0	0.0	0.0	1.3	1.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	2.0	1.3	1.0
Lang																							
Naming	30.0	29.0	29.0	30.0	29.0	26.0	29.0	28.0	29.1	30.0	30.0	29.1	29.0	29.0	30.0	29.1	29.1	29.1	29.0	30.0	29.0	29.1	28.0
LR																							
RPCM	32.8	30.9	32.7	29.7	32.5	29.6	36.0	36.0	26.8	36.0	33.5	36.0	30.5	30.6	32.2	34.0	36.0	31.4	32.3	25.2	32.8	36.0	29.1
CP																							
CD	10.3	10.9	10.8	9.3	12.0	12.0	12.0	12.0	12.0	12.0	9.2	12.0	10.1	10.0	12.0	12.0	12.0	12.0	10.9	9.1	10.6	12.0	8.6
CDWL	70.0	68.9	69.8	70.0	70.0	70.0	70.0	70.0	70.0	70.0	70.0	70.0	68.1	68.3	70.0	70.0	70.0	70.0	68.2	67.8	68.5	70.0	68.7
CRF-C	34.9	31.5	36.0	32.7	32.7	34.5	32.7	33.1	33.7	28.8	28.9	32.7	32.9	33.1	32.4	24.0	32.7	33.9	31.9	33.4	36.0	32.7	33.0

	HE	HE	HE	HE	HE	HE	HE	HE	HE	HE
	24	25	26	27	28	29	30	31	32	33
MMSE	30.0	27.9	27.2	30.0	30.0	28.5	30.0	30.0	29.3	26.5
V-LTM										
15WL-IR	42.9	45.5	41.6	30.3	42.9	40.6	31.2	57.7	56.0	36.1
15WL-DR	10.9	9.0	9.0	12.4	10.9	6.0	7.9	10.7	10.0	7.2
15WL-HR	14.0	14.0	15.0	14.0	15.0	14.0	12.0	13.0	14.0	13.0
15WL-FA	1.4	1.0	2.0	1.4	0.0	1.0	1.0	0.0	1.4	4.0
SS-IR	6.2	6.0	6.3	6.2	5.8	6.2	6.0	3.9	6.2	7.7
SS-DR	6.1	6.1	6.2	6.1	5.8	6.1	5.8	4.0	6.1	8.0
VS-LTM										
CRF-IR	15.8	24.0	10.5	15.8	8.4	10.2	15.6	13.3	15.8	23.0
CRF-DR	15.2	15.8	10.1	15.2	14.6	14.1	15.9	11.5	15.2	23.2

V-STM AND V-WM										
DS-F	6.4	4.4	4.8	5.5	8.3	4.8	6.4	5.4	6.5	3.8
DS-B	6.0	5.0	4.0	4.0	5.0	4.0	4.0	4.0	5.0	4.0
VS-STM and VS-WM										
CBT-F	4.7	6.1	4.0	6.8	6.5	5.0	4.1	4.0	5.3	4.0
CBT-B	5.3	6.0	4.0	5.3	4.0	5.0	4.0	3.0	5.3	5.0
EXE-F										
PVF	51.6	33.6	29.3	49.0	36.9	31.3	50.5	22.3	38.9	18.6
MCST-CA	5.9	6.0	6.0	5.9	6.0	6.0	6.0	5.0	5.9	5.0
MCST-PE	1.3	1.0	1.3	1.3	0.0	0.0	2.0	0.0	1.3	8.0
Language										
Naming	29.1	29.0	30.0	29.1	29.0	29.0	28.0	28.0	29.1	30.0
LR										
RPCM	32.5	36.0	36.0	32.4	29.6	28.8	30.8	32.6	36.0	31.1
CP										
CD	12.0	11.1	10.6	11.0	9.6	8.6	12.0	8.0	12.0	10.0
CDWL	70.0	69.4	70.0	70.0	69.0	67.5	69.3	70.0	70.0	70.0
CRF-C	34.0	33.3	32.7	32.6	32.4	34.6	34.2	30.1	32.7	35.6

Abbreviations: 15-WL-IR= 15-Word List-Immediate Recall; 15-WL-DR= 15-Word List-Delayed Recall; 15-WL-HR= 15-Word List-Hit Rates; 15-WL-FA= 15-Word List-False Alarms; CRF-C= Complex Rey's Figure-Copy; CRF-IR= Complex Rey's Figure-Immediate Recall; CRF-DR= Complex Rey's Figure-Delayed Recall; CBT-F= Corsi Block Tapping test Forward; CBT-B= Corsi Block Tapping test Backward; CD= Copy of drawings; CDWL= Copy of Drawing With Landmarks; CP= Constructional Praxis; DS-F= Digit span Forward; DS-B= Digit span Backward; EXE-F= Executive functions; Lang= Language; LR= Logical Reasoning; MMSE=Mini Mental State Examination; MCST-CA= Modified Card Sorting Test-Criteria Achieved; MCST-PE= Modified Card Sorting Test-Perseverative Errors; PVF= Phonological Verbal Fluency; RPCM= Raven's Progressive Coloured Matrices; SS-IR= Short Story- Immediate Recall; SS-DR= Short Story- Delayed Recall; V-LTM= Verbal Long-Term Memory; VS-LTM=Visuo-spatial Long-Term memory; V-STM= Verbal Short-Term Memory; V-WM= Verbal-Working Memory; VS-STM= Visuospatial-Short-Term Memory; VS-WM= Visuospatial-Working Memory.

Cut-offs: 15-WL-IR cut-off>28.5; 15-WL-DR cut-off>4.6; CD cut-off>7.1; CDWL cut-off >61.8; CRF-C cut-off >23.7; CRF-IR cut-off>6.4; CRF-DR cut-off>6.3; CBT-F cut-off>3.5; CBT-B cut-off>3.0; DS-F cut-off>3.7; DS-B cut-off>2.6; MCST-CA cut-off>4.2; MCST-PE cut-off>7.6; MMSE cut-off >23.7; Naming cut-off>22; PVF cut-off>17.1; RPCM cut-off>18.9; SS-IR cut-off>3.1; SS-DR cut-off>2.8.

See text for further details