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

Introduction

Subjective Cognitive Decline (SCD) is a condition defining individuals who perceive a decrease in their own cognitive functioning in the absence of any objective cognitive impairment detectable on standard neuropsychological testing [1]. Over the last decades, there has been growing interest in SCD as an early stage of cognitive decline. This is due to the increased risk of SCD individuals to develop mild cognitive Impairment and to eventually convert to dementia [2, 3]. In 2014, the international SCD-initiative (SCD-I) working group defined a standardised terminology alongside clinical research criteria for the identification of individuals with SCD. Criteria include the following key features: a self-experienced decline in cognitive functioning over time against a previous normal cognitive status, and reporting normal scores on standardised neuropsychological tests adjusted for age, sex and education [1]. A proportion of individuals complaining of SCD who require medical consultation show abnormalities in CSF beta-amyloid and/or tau protein levels [4], which are biomarkers for a neurobiological diagnosis of Alzheimer's Disease (AD). According to the classification proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA), SCD may be regarded as the earliest clinical stage of AD [5]. This classification is based on the consideration that AD pathology begins to develop years before appearance of any significant cognitive decline and that an early detection of the disease is critical for effective treatment and prevention. Against this background, diagnostic criteria for AD have been recently revised to include SCD as a potential early symptom of AD [6].

In addition to biomarkers, structural and functional brain alterations have been reported in individuals with SCD. Studies using brain imaging to investigate these alterations have demonstrated that individuals complaining of SCD often show reduced grey matter (GM) volumes in brain regions known to play a key role in memory functions, such as the hippocampus and the parahippocampal gyrus. These structural changes are often accompanied, or preceded, by functional abnormalities in SCD brains [7], with disruption of connectivity in networks associated with memory and cognitive control. Altered (increased or decreased) functional connectivity (FC) was found within the Default Mode Network (DMN) of SCD individuals compared to healthy subjects (HS) [8] or between their DMN and other brain regions such as those belonging to the medial temporal memory system [9] or the hippocampus [10]. Other studies observed FC alterations in the Medial Visual Network [11], Salience Network [12], and changes in Fronto-Parietal Network. Interestingly, the Fronto-Parietal network is implicated in central executive control, cognitive flexibility, and plays a crucial role in cognitive reserve [13].

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

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

Methods

Participants

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

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

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

Neuropsychological assessment

All participants underwent an extensive neuropsychological battery including the following tests :Verbal episodic long-term memory: 15-Word List (Immediate and 15-min Delayed recall) [16]; Short Story test (Immediate and 20-min Delayed recall) [17]; Visuo-spatial episodic long-term memory: Complex Rey's Figure (Immediate and 20-min Delayed recall) [17]; Short-term memory: Digit span and the Corsi Block Tapping task forward and backward [18]; Executive functions: Phonological Word Fluency [16] and Modified Card Sorting Test [19] ; Language: Naming objects subtest of the BADA ("Batteria per l'Analisi dei Deficit Afasici". Italian for "Battery for the analysis of aphasic deficits") [20]; Reasoning: Raven's Coloured Progressive Matrices [16]; Constructional praxis: Copy of drawings [16] and Copy of drawings with landmarks [16]; Copy of Complex Rey's Figure [17]. The individual scores reported by SCD individuals and HS subjects on the neuropsychological battery are reported in Supplementary Tables 1A and 1B.

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

MRI Acquisition

Brain MRI was performed on a 3T scanner (Magnetom Allegra; Siemens. Erlangen, Germany). The acquisition parameters of each MRI acquisition were as follows: (1) Dual-echo turbo Spin Echo (TSE) (repetition time [TR]=6.190 msec; echo time [TE]=12/109 msec); (2) fluid attenuated inversion recovery (FLAIR) (TR=8.170 msec; TE=96 msec.; inversion time [TI]=2.100 msec); (3) T1-weighted 3D MDEFT (TR=1338 ms; TE=2.4 ms; Mmatrix=256x224x17; in–plane FOV=250x250 mm^2; slice thickness=1 mm); (4) T2* weighted echo planar imaging (EPI) volumes sensitized to BOLD contrast (TR=2080 ms, TE=30 ms, 32 axial slices parallel to AC-PC line, matrix=64x64, pixel size=3x3 mm^2, slice thickness=2.5 mm, flip angle:70°). BOLD EPIs were collected during rest for a 7 min and 20 s period, resulting in a total of 220 volumes. During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep.

Medial temporal lobe atrophy and macroscopic brain tissue abnormalities

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

Image analysis for Voxel-based morphometry

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

Image Analysis for resting-state functional MRI

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

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

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

Statistical analyses

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

For voxel-based morphometry, statistical analyses of regional GM volumes were performed in SPM-12 using smoothed GM maps within the framework of the general linear model. A two-sample T-test was employed to assess between group differences (SCD and HS) in either direction. Intracranial volumes (obtained by adding up WM volume + GM volume + CSF volume) were entered in all analyses as a covariate of no interest. In VBM imaging analyses results were accepted as significant at p<0.05 FWE corrected values at cluster level.

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

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

Results

Demographic and clinical characteristics

As reported in Table 1, there were no significant between-group differences in age ($F_{1.54}$=0.04. p=0.842), years of formal education ($F_{1,54}$=0.138. p=0.712), MMSE ($F_{1.54}$=0.65. p=0.420), and MTA scores ($F_{1,54}$=0.029. p=0.866). Sex distribution was different between groups with a higher representation of females in the SCD group (Chi-square=7.1. df=1. p=0.007).

Neuropsychological assessment

As reported in Table 2, at a group level, SCD individuals reported significantly lower scores than HS in the following neuropsychological tests: Short Story test-20 min Delayed recall ($F_{1,54}$=2.871, p=0.007), Corsi Block Tapping backward test ($F_{1,54}$= 7.25, p=0.009), Copy of drawings with landmarks ($F_{1,54}$= 5.20, p=0.026). As mentioned above, all these scores were used to assess possible associations with measures of FC (covariates of interest) in each group separately.

Voxel-based morphometry

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

Resting-state fMRI

There were no significant differences between groups in the mean motion parameters 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, F_1=0.03, p=0.860).

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

Cross-sectional analysis

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

Associations between functional brain connectivity and cognitive measures

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

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

Discussion

The present study aimed at investigating potential associations between cognitive measures and structural and functional brain alterations in individuals with SCD.

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

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

[31]. These findings suggest that working memory deficits may be an early marker of cognitive decline, and a potential target for early intervention in SCD. Taken together all these results indicate an early difficulty of SCD individuals in engaging their executive functions. In our hypothesis, SCD individuals do not suffer from a specific pattern of cognitive impairment, but rather show a general difficulty to access their executive system. This may indeed be responsible itself for the cognitive deficits that SCD individuals subjectively experience. Executive dysfunctions have been previously described in SCD populations [32-34]. Impairment of higher executive abilities, such as the divided attention or flexibility, may impact on free recall during memory tasks [33, 35].

In the present study we did not find any brain volumetric changes in SCD individuals compared to HS. In the literature there have been reported controversial results on this subject. Some studies reported decreased hippocampal volume in SCD subjects [36, 37, 38, 39, 40], while other studies failed in identifying any significant hippocampal atrophy [41, 42, 43, 44, 45]. This might be explained by a high heterogeneity of SCD individuals, whose mismatch between regional brain volumetrics and symptoms may be accounted in either direction by other factors, such as cognitive reserve [46].

Conversely, in the current study we identified significant differences between SCD individuals and HS in functional brain connectivity within the FPN and CEN, which are regard as networks critically involved in cognition [47-48]. When looking at the FPN, individuals with SCD showed FC changes in either direction within the right hippocampus and the parahippocampal gyrus bilaterally, and increases in left angular gyrus. These findings are consistent with the well-known notion that the hippocampus and medio-temporal cortices are involved in the encoding, storage and retrieval of long-term memory traces [49]. In addition, the left angular gyrus has been previously associated with higher level functions, including memory and awareness [50]. We might argue that the decrease of FC in the hippocampus and its increase in the angular gyrus might account for the memory difficulties that are subjectively experienced by SCD individuals. Additionally, reduced FC of the hippocampus might explain why SCD individuals retrieve items incorrectly, while increased FC of the angular gyrus might be interpreted as a compensatory mechanism against hippocampal failure in driving memory performance into the normal range. Finally, increased FC of the angular gyrus might explain why individuals with SCD are subjectively aware of their own cognitive difficulties.

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

When looking at the FPN in HS in isolation, we found a positive association between their Corsi span blocking test scores and FC in the supplementary motor cortex and in the left cingulate gyrus. This finding is in line with the observation that several motor regions, including the supplementary motor area, are simultaneously engaged in working memory tasks [57-58]. Unfortunately, the Corsi span blocking test does not allow us to disentangle between different modules involved in the working memory function. According with Baddley [59, 60], working memory functions involve the central executive system, the phonological loop and the visuospatial sketchpad. We can only hypothesise that the CEN may differently control the central executive system and the visuospatial sketchpad, thus contributing to their normal functioning in healthy subjects. Finally, HS showed a positive association between performance at the Copy of drawings with landmarks task and FC of the Cingulate gyrus, within the CEN. The cingulum has been previously found to be involved in the correct execution of constructional praxis tasks [61]. Deficits in constructive praxis are regarded as a hallmark of AD, and have been linked to dysfunction in the posterior parietal and in the prefrontal cortex [61]. Interestingly, the cingulum plays a critical role in connecting each other these different parts of the brain.

Our imaging findings went in either direction, an increase or a decrease of functional connectivity within networks. A classical neurobiological interpretation of decreases and increases of connectivity are network disruption in the former case and compensatory mechanisms of brain plasticity in the latter case [62-64]. Main contribution to this interpretation comes from longitudinal studies, which documented an increase of functional connectivity passing from mild cognitive impairment status to dementia [65-67].

One of the limitations of the present study is the absence of any neurobiological markers (e.g., CSF; PET imaging) for the diagnosis of AD in our cohort. Nonetheless, cognitive profile and brain connectivity were significantly different between SCD subjects and controls, reinforcing the idea that former group diverts from a "healthy pathway". Another limitation of this study is the relatively small sample-size, which requires future confirmatory studies on larger populations. Partially related to this point, there a mismatch between males and females in the two groups, due to consecutive recruitment of patients. Despite out of the scope of the present study, such a mismatch would also deserve to be further investigated itself in the framework of gender differences in response to the same pathological condition. However, our sample size does not allow such an additional analysis. Future studies on larger populations are needed.

In conclusion, the present study contributes in considering SCD as a high risk condition for developing AD over time. Biomarkers of AD pathology, as well as alterations in brain structure and function, have been previously described in SCD individuals, with remarkable implications for an early detection and treatment of AD. Brain connectivity, appears as a potential sensitive tool for patient stratification and clinical trial monitoring.

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Conflict of interest

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Data Availability" statement

All data are available contacting the Santa Lucia Foundation IRCCS

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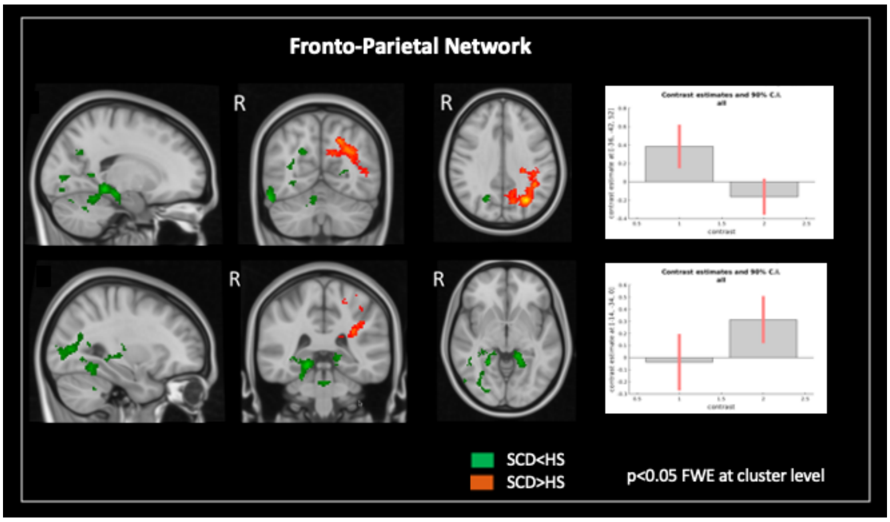
Figures

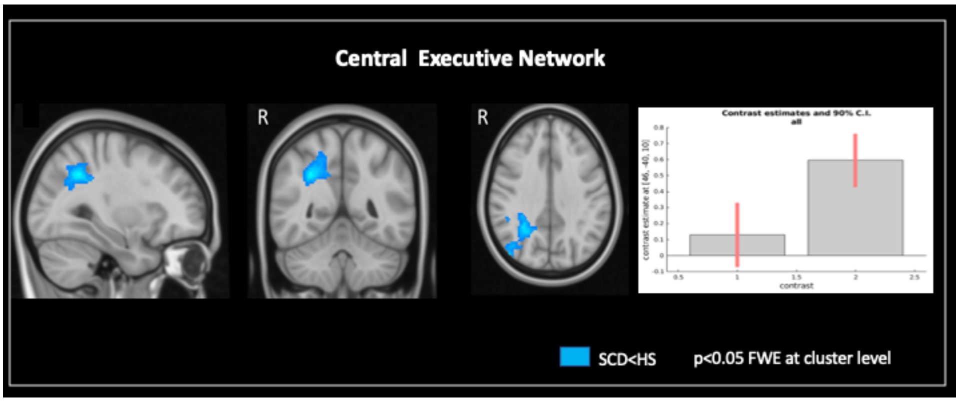
Figure 1.



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.

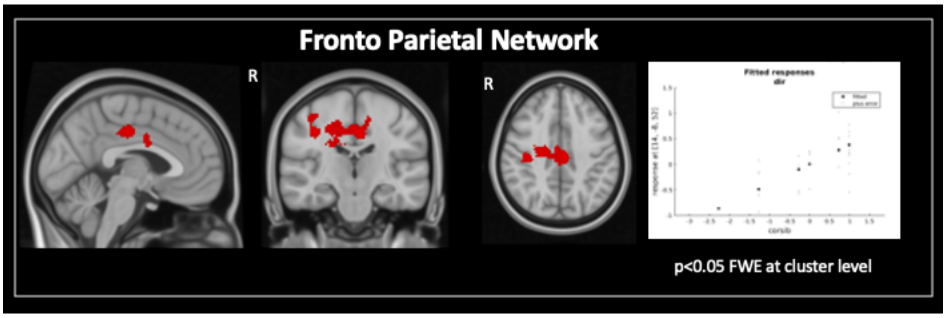
Figure 2.



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.

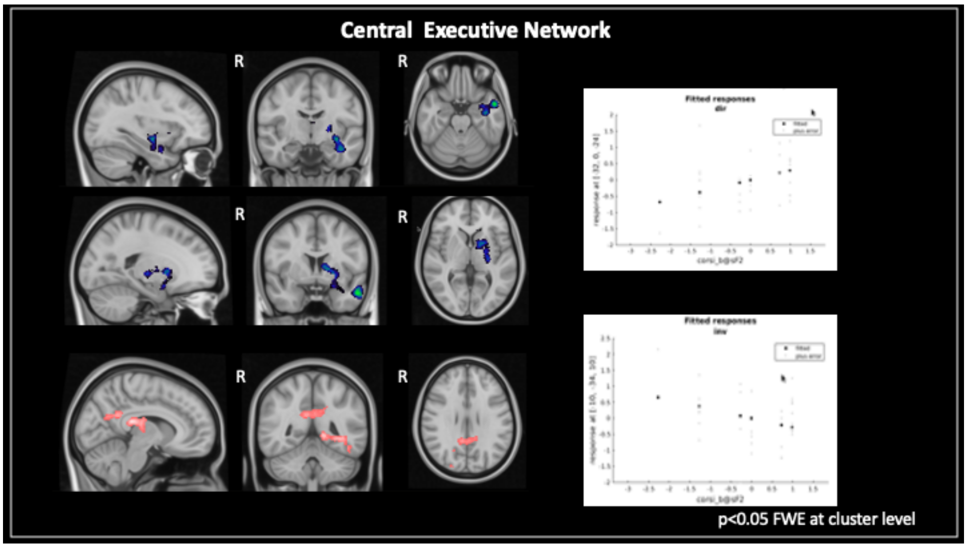
Figure 3.



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.

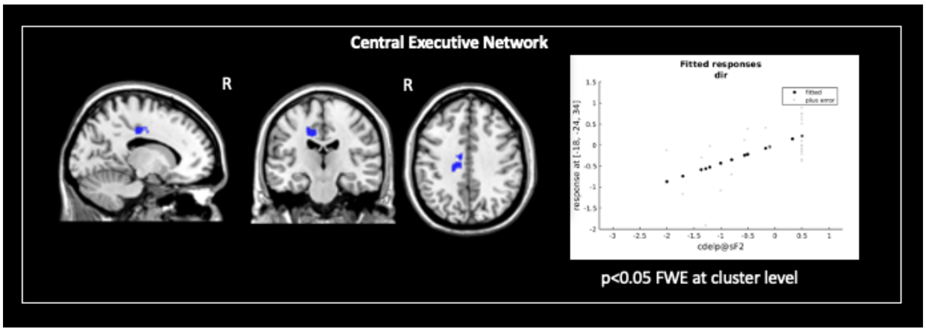
Figure 4.



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.

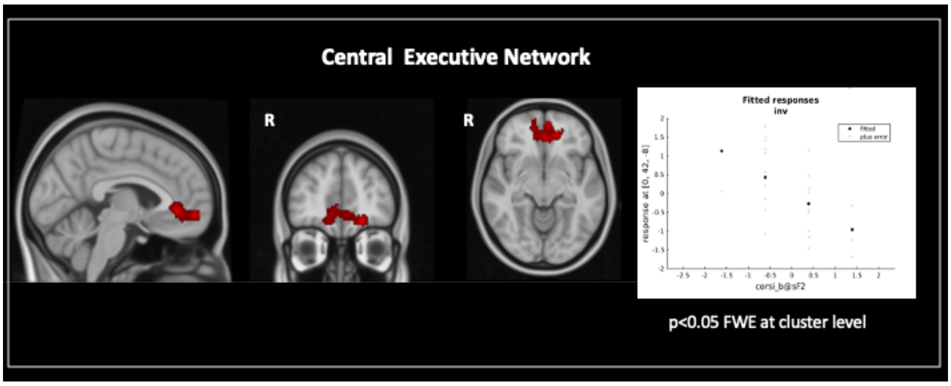
Figure 5.



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 (N=23)	**HS** (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 IR mean (SD)	43.6 (7.5)	45.9 (9.1)	0.302
	15-Word List 15-min DR mean (SD)	9.0 (2.4)	9.7 (2.2)	0.302
	15-Word list Recognition hit-rates mean (SD)	13.2 (1.8)	13.9 (0.9)	0.059
	15-Word list Recognition false mean (SD)	1.1 (1.6)	1.4 (1.2)	0.471
	Short Story Immediate recall mean (SD)	5.6 (1.1)	6.1 (1.1)	0.096

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

Working Memory				
	Corsi Block Tapping forward mean (SD)	5.0 (0.6)	5.0 (0.8)	0.989
	Corsi Block Tapping backward mean (SD)	4.6 (0.8)	5.3 (0.9)	0.009
Executive functions				
	Phonological verbal fluency Mean (SD)	34.3 (10.6)	36.7 (9.1)	0.364
	Modified Card Sorting test Criteria achieved mean (SD)	5.8 (0.6)	5.9 (0.3)	0.402
	Modified Card Sorting test Perseverative errors mean (SD)	1.3 (1.8)	1.3 (1.9)	0.928

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								
	SCD<HE	Parahippocampal gyrus	L	3640	3.09	-18	-24	-18
		Hippocampus	R		2.51	22	-37	6
		Parahippocampal gyrus	R		1.28	22	-50	4
	SCD>HE	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	*SCD<HE*	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.

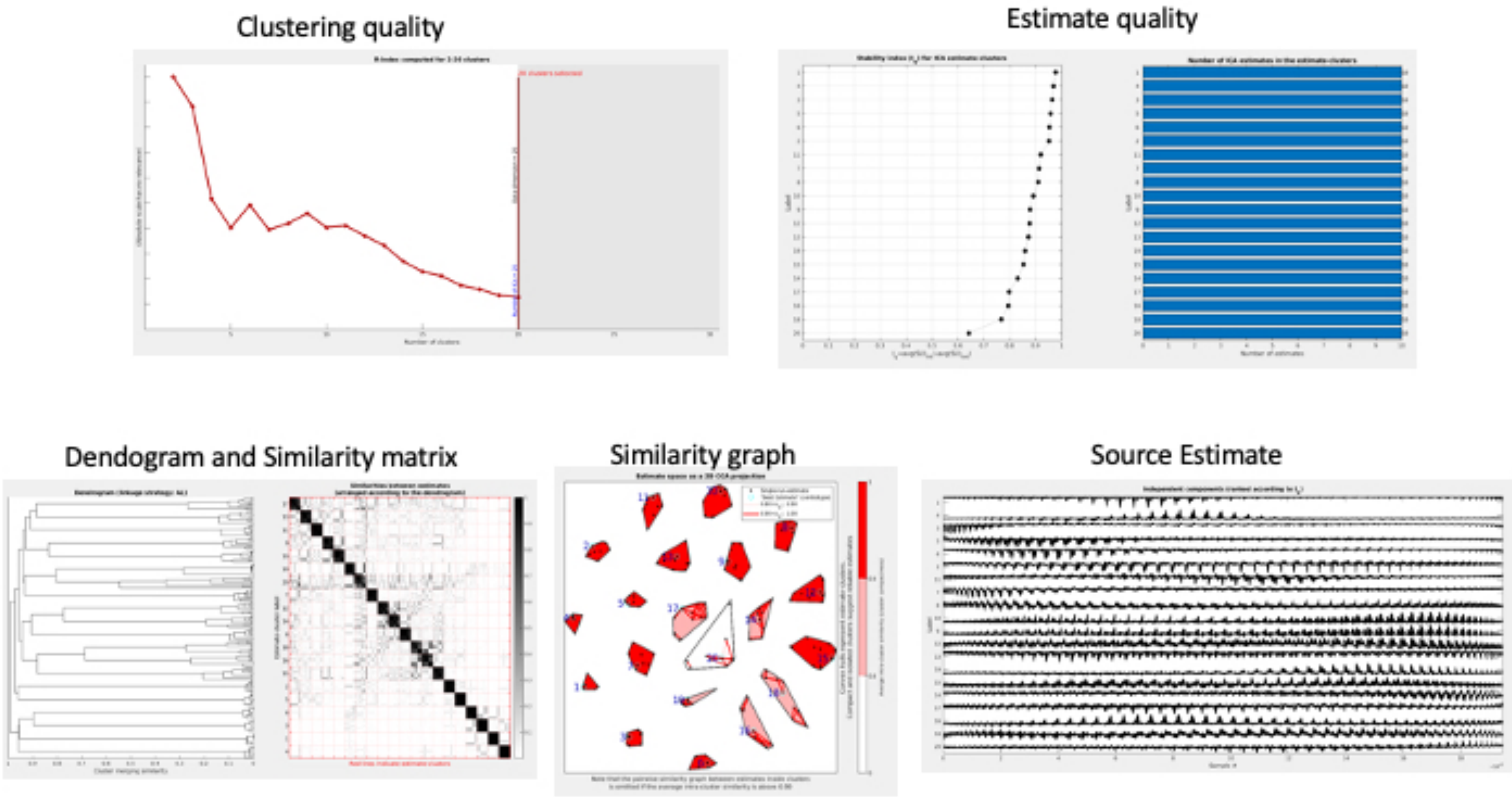
Brain network	Cognitive tests	association	Brain regions	Side	Size	Z-score	MNI coordinates (mm)		
							x	y	z
FPN	*Corsi block tapping test*	Positive	Supplementary motor cortex	R	2016	4.30	14	-8	52
			Cingulate gyrus	L		3.39	-6	-22	38
CEN	*Corsi block tapping test*	Positive	Middle temporal gyrus	L	1795	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 Drawings with landmarks	Positive	Cingulate gyrus	L	176	4.53	-16	-22	42

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	*Corsi block tapping test*	Negative	Cingulate gyrus	R	1638	3.52	2	40	-4

Supplementary Figure 1.



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																							
15WL-IR	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
15WL_DR	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
15WLi-HR	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
15WL-FA	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
SS-IR	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
SS-DR	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																							
CRF-IR	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
CRF-DR	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																							
DS-F	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
DS-B	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																							
CBT-F	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
CBT-B	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																							
PVF	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
MCST-CA	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

MCST-PE	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 *Naming*	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 *RPCM*	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																							
CD	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
CDWL	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
CRF-C-	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 1	HE 2	HE 3	HE 4	HE 5	HE 6	HE 7	HE 8	HE 9	HE 10	HE 11	HE 12	HE 13	HE 14	HE 15	HE 16	HE 17	HE 18	HE 19	HE 20	HE 21	HE 22	HE 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 24	HE 25	HE 26	HE 27	HE 28	HE 29	HE 30	HE 31	HE 32	HE 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

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