

Do 2-year changes in superior frontal gyrus and global brain atrophy affect cognition?

Authors:

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http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Abstract

Metabolic alterations to the superior frontal gyrus (SFG) have been linked to cognitive decline and transition from Mild Cognitive Impairment to Alzheimer's disease(AD). Whether these indicate structural atrophy, which could be screened for at a larger scale using non-invasive structural imaging is unknown. We assessed annual structural MRI scans and cognitive data from 3 consecutive years from 204 participants from the AD Neuroimaging Initiative database (mean age 72.24(8.175) years). We evaluated associations between brain structural changes and performance in the Montreal Cognitive Assessment, Everyday Cognition visuospatial subtest (Ecog Visuospatial) and Functional Assessment Questionnaire.

Keywords

Brain, MRI, superior frontal gyrus, brain atrophy, cognitive decline

1. Introduction

Disorders of cognition continue to provide profound social and economic challenges to society with our ever increasing elderly population. Cognitive decline in adulthood represents a continuum ranging from normal healthy ageing to mild cognitive impairment (MCI) to dementia with growing severity in each cognitive grouping. Cognitive decline has been associated with a global decrease in brain volume proportionate to the degree of decline seen [1]. One hallmark of cognitive decline is deficits in executive functioning affecting skills such as working memory, multitasking and attention [2]. The prefrontal cortex has been widely associated with these functions and therefore linked to progression of overt manifestation of cognitive dysfunction.

A study using positron emission tomography (PET) scanning found that metabolic changes in the prefrontal cortex, including the superior frontal gyrus (SFG), were present in patients with MCI that progressed to Alzheimer's Disease (AD) and absent in non-progressors [3]. Given the invasiveness and expense of PET scanning, this study has limited clinical applicability but indicated that there are specific areas of the brain that may be of interest in evaluating markers that could be better indicators of the changes across the continuum of cognitive decline, and that the SFG could be one of these areas. Structural imaging modalities such as MRI would overcome these practical barriers with their ease of use, non-invasiveness and relatively low cost [4].

The SFG is known to be heavily involved in a variety of cognitive and motor control tasks. The lateral part is thought to have strong associations with working memory and attention, with the medial being more influential in other cognitive-related processing [5;6]. In addition to the study from Dzerga and colleagues, biochemical and structural changes on this brain region have been seen in other diseases that affect cognitive performance such as Parkinson's Disease and Schizophrenia [6]. Cortical thickness is known to be a very stable parameter [7] which illustrates cellular characteristics such as myelination, cell size and the number of cortical neurons [8]. Previous studies have used changes in cortical thickness to separate patients of different cognitive capacity and to examine the differences between MCI 'progressors' and 'non-progressors' [7]. Decrease in the SFG cortical thickness has been associated with declining cognition [7]. Furthermore, cortical surface area has been well established as a sensitive marker to brain structure changes [9]. In normal ageing, it is known that the SFG has one of the greatest age-related surface area reductions in the brain [10]. Reductions in the surface area have been shown to correlate with low working memory performance in healthy populations, however this has currently not been established in the context of cognitively impaired

demographics [9] and to the best of our knowledge, it has not been analysed in the context of progression to any form of dementia.

Therefore, the goal of this study was to investigate whether changes in global brain atrophy and SFG structural measurements were associated with worsen in performance on cognitive tests that assessed tasks been known to be sensitive to cognitive group differentiation and indicative of steep cognitive decline. The ultimate aim of the study was to add to the search for structural brain imaging markers sensitive to cognitive performance that could be used for early AD diagnosis.

2. Materials and methods

2.1 Subjects

Data was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), a large scale, longitudinal, ongoing collaborative study running since 2004 focused on finding biomarkers to assist in the diagnosis and prognosis of cognitive decline (ADNI, 2017). Subjects, aged 55-90, were selected from 55 sites in the United States and Canada including cognitively normal (CN) subjects, patients with early mild cognitive impairment (EMCI), others with late mild cognitive impairment (LMCI) and AD patients. Further information about the ADNI study and detail about selection criteria and protocols, can be found at <http://adni.loni.usc.edu/methods/documents/>. The database was accessed in January 2017.

At the time of accessing the database, 204 subjects (IDs given in Annex 1 for reproducibility purposes) with the following selection criteria were identified:

- Three consecutive scans acquired exactly 12 months apart
- Complete structural MRI data sets with T1-weighted, T2-weighted, T2*-weighted and Fluid Attenuated Inversion Recovery MRI sequences at each visit
- Cognitive assessments done at the time of each MRI scan

The selection and image processing of the MRI scans were done blind to any clinical, demographic or cognitive status/data.

2.2 Cognitive Assessments

All participants undertook a wide range of cognitive tests as described in <http://adni.loni.usc.edu/data-samples/clinical-data/> and <http://www.adni-info.org/Scientists/CognitiveTesting.html>. For this study we used the Functional Activities Questionnaire (FAQ), Montreal Cognitive Assessment (MoCA) and Everyday Cognition (ECog) Visuospatial tests, all which were available for all selected participants at the imaged time points. Each participant's cognitive status (i.e. Cognitively Normal (CN), Early Mild Cognitive Impaired (EMCI), Late Mild Cognitive Impaired (LMCI), and Alzheimer Disease (AD)) was determined from the results from the Mini Mental State Exam (MMSE), Clinical Dementia Rating (CDR) score and the Logical Memory (II) component of the Wechsler Memory Scale [11], as described in [12].

2.3 MRI acquisition

All images were acquired at 3T scanners. Turbo Spin Echo (TSE) T2-weighted images were acquired axially, with TE/TR=80/3000 ms, flip angle 90°, matrix 256 x 256 x 44, voxel size 0.9375 mm x 0.9375 mm x 4 mm. 2D FLAIR images were also acquired in axial orientation, with TE/TR/TI=90/9000/2500 ms, matrix 256 x 256 x 35, voxel size 0.8594 mm x 0.8594 mm x 5 mm. 2D axial T2*-weighted images were acquired with TE/TR=20/650.001 ms, matrix 256 x 256 x 44, voxel size 0.7812 mm x 0.7812 mm x 4 mm, and 3D T1-weighted MPRAGE sequences were acquired sagittally with TE/TR=3.162/6.818, flip angle 9°, matrix 256 x 256 x 170, voxel size 1 mm x 1 mm x 1.2 mm. These sequence parameters were consistent with little variations across the sites. More information about the (ADNI-2 and ADNI-go) MRI imaging protocols can be found in: <http://adni.loni.usc.edu/methods/documents/mri-protocols/>.

2.4 Image Analysis

T1-weighted, FLAIR and T2*-weighted images were spatially rigidly and automatically aligned to the T2-weighted using FLIRT (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT>). The intracranial contents were extracted also fully automatically using BRICbet, a MATLAB function publicly available, which is part of the library BRIClib (https://sourceforge.net/projects/bric1936/files/MATLAB_R2015a_to_R2017b/BRIClib/). It uses either the susceptibility-weighted image (i.e. T2*-weighted) or a combination of it with a T2-weighted-based image (i.e. T2-weighted and/or FLAIR), on a pipeline that involves bias field correction and brain extraction using BET2 (<http://poc.vl-e.nl/distribution/manual/fsl-3.2/bet2/index.html>), followed by first order statistical manipulations of the intensity of the brain extracted volume, combined with morphological operations. Total CSF volume and pial structures

(e.g. veins and meninges) were obtained fully automatically from the MRI scans using multispectral Gaussian Clustering (i.e. clustering based on Gaussian Mixture Models using the Expectation-Maximization algorithm). Brain Ventricles were extracted using non-linear registration of the regional brain atlas for assessment of white matter hyperintensities

(<http://datashare.is.ed.ac.uk/handle/10283/2217>) combined with the total CSF mask (i.e. which also included pial structures), also fully automatically as per [13]. All resultant binary masks were visually inspected and manually corrected only if and where required using Mango

(<http://ric.uthscsa.edu/mango/index.html>).

Preliminary analyses of automatic segmentations of the superior frontal cortex yielded inconsistencies in its boundaries for different subjects. Therefore, ground truth segmentations of the superior frontal cortex, were generated on a randomly selected subsample of datasets from 34 subjects following a detailed protocol based on the Ono [14] and Duvernoy [15] brain atlases and considering the recommendations from Mikhael et al. (2017)[16]. Every SFG was delineated by drawing 2 open curves; an outer curve for the grey matter boundary with the subarachnoid space (red) and another demarcating the inner white matter boundary of the gyrus as Figure 1 shows. The cortices were segmented on axial slices of each scan manually using mricron

(<https://www.nitrc.org/projects/mricron/>).

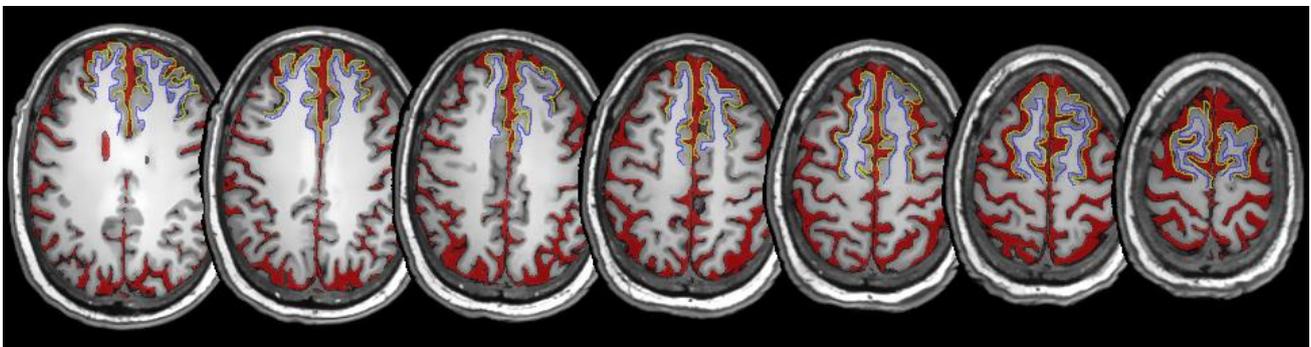


Figure 1. Axial T1-weighted slices showing the results of the CSF and Superior Frontal Gyrus Cortex segmentations. Red represents ventricular and Total CSF. Yellow represents grey matter outer boundary of the SFG whilst blue represents white matter outer boundary of the SFG.

All measurements were done independently at the three time points: year 1 (Y1), year 2 (Y2) and year 3 (Y3). The SFG outer boundary was used to calculate the cortical surface area. The cortical thickness was calculated using the distance transform of the cortex in the region delineated, which calculates the Euclidean distance between the inner and outer boundaries of the SFG at each point.

Average values of the manual segmentations were used in the analyses. SFG cortical volumes were calculated by multiplying the SFG surface area by the SFG cortical thickness.

2.5 Statistical analyses

Cerebrospinal fluid (CSF) was used as a proxy for brain atrophy as any increase in atrophy would equally give concomitant increases in CSF volume. We calculated the change in cognitive performance and brain atrophy measurements (i.e. Ventricular CSF Volume, Total CSF Volume, and SFG volume all adjusted for head size, Average Surface Area of the SFG, and Mean Cortical Thickness of the SFG), as the difference between the measurements acquired at two different years, e.g. (Y2-Y1), (Y3-Y2) and (Y3-Y1). Any positive results in the global imaging variables and any negative results in the local SFG measurements indicates an increase in global/local atrophy respectively. For the analyses, all brain volumetric measurements were adjusted for head size by calculating the percentage they represent in ICV. We performed linear regression analyses evaluating fitness to a general linear model using MATLAB R2014b (stepwiseglm function), to assess the association between the yearly changes of the atrophy variables obtained, and the changes in the performance in the selected cognitive tests, controlling for the confounding effects of age. If an association was found, other covariates were subsequently added to the initial model to establish the extent and conditions of the associations. These were: gender, baseline cognitive performance in the mini-mental state examination test, years of education, family history of dementia/AD, cardiovascular and endocrino-metabolic risk factors. We used backwards step-wise general linear models to evaluate the results of our linear model, and appraised the model fitness while adding or removing variables using both: the Akaike Information Criterion and the p -value for the chi-squared test of the change in the deviance by adding or removing the term. The model with all possible interactions was the largest model to consider in the evaluation. Paired samples t-test and correlations were calculated using IBM SPSS Statistics ver. 21 (release 21.0.0.0, 64 bit ed.) to evaluate differences between variables and changes between years (non-standardised correlation coefficients B and p values given). The results were re-evaluated doing a percentile bootstrap on the pair difference and adjusted for multiple comparisons using the Robust Statistical MATLAB Toolbox ([17] – MATLAB implementation, in [//github.com/Cpernet/Robust_Statistical_Toolbox](https://github.com/Cpernet/Robust_Statistical_Toolbox)). Finally, Neurosynth (<http://www.neurosynth.org/>) was used to investigate on the positive associations found. Neurosynth is a platform for automatically synthesising the results of meta-analysing thousands of neuroimaging studies[18]. We queried the term-based meta-analyses database for the cognitive function(s) that resulted associated with the brain imaging variable(s) analysed. Such query triggers a giant meta-analysis comparing the coordinates reported for studies with and without the term entered, producing statistical inference maps and posterior probability

maps that display the likelihood of a given term being used in a study if activation is observed at a particular voxel.

3. Summary of the Data

The sample included 71 cognitively normal (CN), 65 early MCI (EMCI), 61 late MCI (LMCI) and 7 AD ADNI participants mean age of 72.24 (8.175) years old. Age, gender and years of education were balanced among cognitive groups. Detailed demographics for each cognitive group can be seen in supplementary table S1 (Annex 2). The median number of cardiovascular risk factors (0: none, 1: cardiovascular disease or smoking, 2: both) was 1 across the 4 cognitive groups. None of the individuals that provided data for this analysis changed the cognitive group within the period analysed.

The descriptive statistics of the imaging and cognitive parameters explored are shown in Table 1 and illustrated in Figures S2-S10 of Annex 2.

Box plots like the ones shown in Figure 2 can be obtained from running the matlab scripts:

- 1.- General_atrophy_related_stats.m
- 2.- SFG_related_stats.m
- 3.- SFG_related_stats_extended.m

The second and third script are similar, and are both included for academic teaching purposes.

From the 204 individuals pseudo-randomly selected, only 177 had all variables to explore associations between changes in the imaging (i.e. global brain atrophy) parameters and changes in the outcome of the cognitive tests selected.

Figure 3 was generated with the script SFG_related_stats.m

The list of all the references consulted during this study are given at the end of this document.

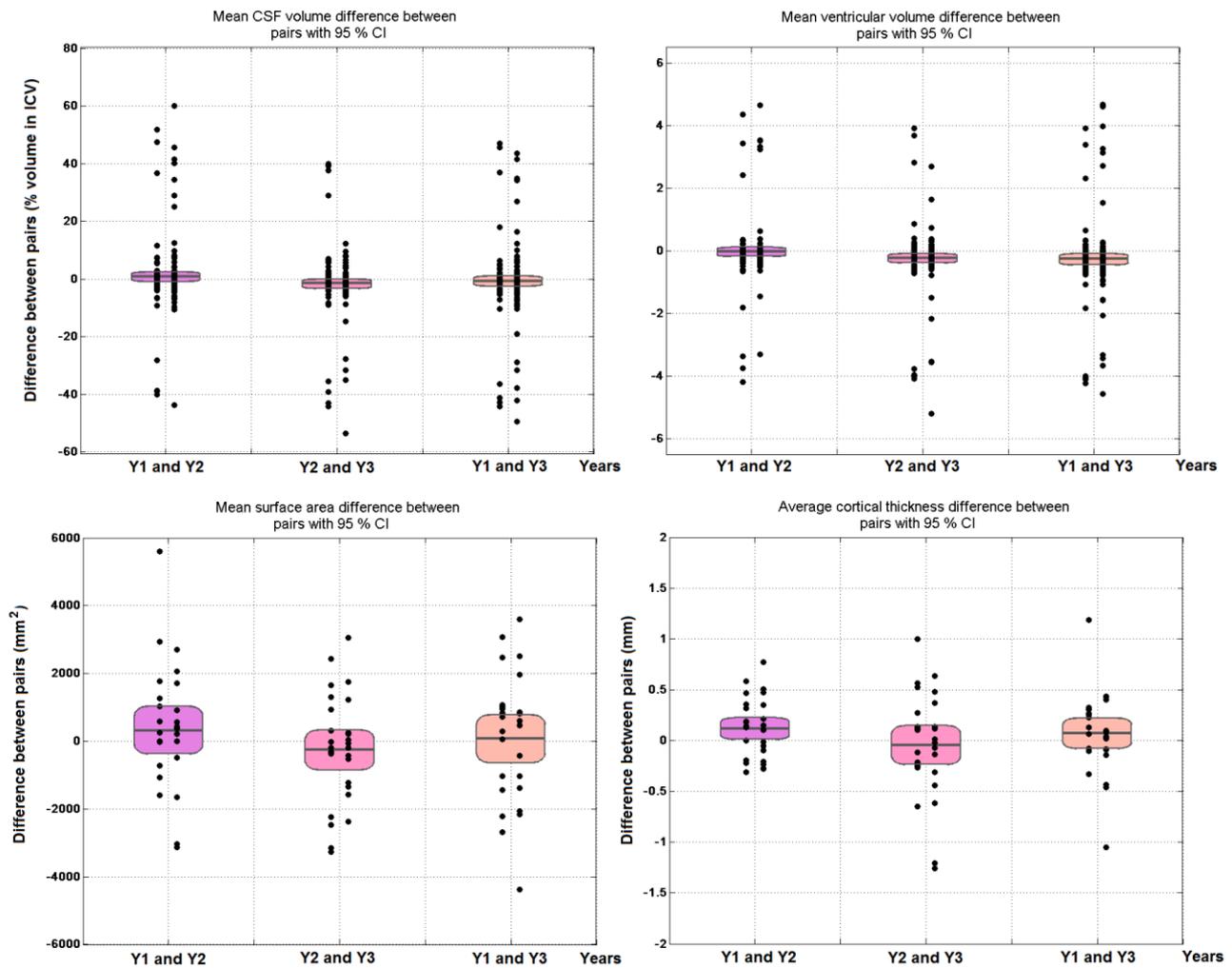


Figure 2. Paired differences of the brain MRI measurements took on two consecutive years (first two columns from left to right) and two years apart (third column from left to right) after being adjusted for head size (i.e. % in ICV) show significance in the transitions from years 1 and 2 to 3 even after correcting for multiple comparisons.

Table 1. Descriptive Statistics of the imaging and cognitive variables used. The “-“ sign represents average decrease of the parameter in a year (Y) / 2-year time.

Cognitive group	Parameter	n	Mean (SD)		
			Y1 → Y2 (i.e. Y2-Y1)	Y2 → Y3 (i.e. Y3-Y2)	Y1 → Y3 (i.e. Y3-Y1)
CN	Total CSF (% in ICV)	67	-1.74 (13.78)	1.62 (12.67)	-0.12 (13.53)
	Ventricular CSF (% in ICV)		-0.05 (1.20)	0.22 (1.21)	0.17 (1.35)
	Average SFG surface area (mm ²)	12	-529.92 (1389.19)	695.97 (1412.53)	135.33 (1405.31)

	Mean SFG cortical thickness (mm)		-0.11 (0.21)	-0.10 (0.44)	-0.23 (0.37)
	SFG volume (% in ICV)		-0.26 (0.51)	-0.16 (0.69)	-0.47 (0.84)
	FAQ	65	0.34 (2.57)	-0.11 (0.61)	0.23 (2.68)
	MoCA		0.32 (5.65)	-0.26 (4.76)	0.06 (5.57)
	ECogVisuospatial		0.11 (2.89)	0.20 (2.88)	0.31 (3.23)
EMCI	Total CSF (% in ICV)	60	-1.08 (10.52)	1.73 (10.48)	0.65 (12.49)
	Ventricular CSF (% in ICV)		0.09 (0.94)	0.23 (1.05)	0.32 (1.16)
	Average SFG surface area (mm ²)	10	308.07 (1573.98)	609.77 (1092.89)	768.59 (1864.95)
	Mean SFG cortical thickness (mm)		-0.08 (0.26)	0.22 (0.57)	0.13 (0.49)
	SFG volume (% in ICV)		-0.0046 (0.44)	0.35 (0.29)	0.30 (0.74)
	FAQ	57	1.03 (3.19)	0.67 (3.05)	1.70 (4.32)
	MoCA		-0.19 (6.56)	0.58 (4.77)	0.39 (7.03)
	ECogVisuospatial		1.79 (4.36)	-1.10 (4.36)	0.68 (4.24)
LMCI	Total CSF (% in ICV)	55	1.26 (10.38)	0.90 (9.51)	2.16 (10.76)
	Ventricular CSF (% in ICV)		0.11 (0.81)	0.22 (0.65)	0.33 (1.04)
	Average SFG surface area (mm ²)	10	-264.88 (2571.63)	-116.05 (1964.07)	-857.12 (1868.00)
	Mean SFG cortical thickness (mm)		-0.14 (0.39)	0.12 (0.53)	-0.03 (0.25)
	SFG volume (% in ICV)		-0.22 (0.50)	0.11 (0.45)	-0.23 (0.68)
	FAQ	54	0.68 (3.16)	1.96 (4.08)	2.65 (5.21)
	MoCA		0.04 (6.67)	-1.81 (7.27)	-1.78 (8.27)
	ECogVisuospatial		-1.28 (6.54)	1.59 (5.43)	0.31 (7.15)
AD	Total CSF (% in ICV)	7	-5.62 (17.68)	1.96 (1.30)	-3.66 (17.67)
	Ventricular CSF (% in ICV)		-0.30 (1.34)	0.28 (0.27)	-0.02 (1.39)
	Average SFG surface area (mm ²)	2	-557.58 (3.67)	-1900.96 (1624.75)	-2458.54 (1621.08)
	Mean SFG cortical thickness (mm)		-0.10 (0.21)	-0.21 (0.39)	-0.31 (0.17)
	SFG volume (% in ICV)		-0.19 (-0.17)	-0.60 (0.69)	-0.79 (0.52)
	FAQ	3	4.33 (2.89)	4.33 (1.15)	8.67 (4.04)
	MoCA		-2.67 (7.23)	-10.00 (14.42)	-12.67 (10.02)
	ECogVisuospatial		-2.33 (6.11)	9.33 (10.60)	7.00 (5.20)

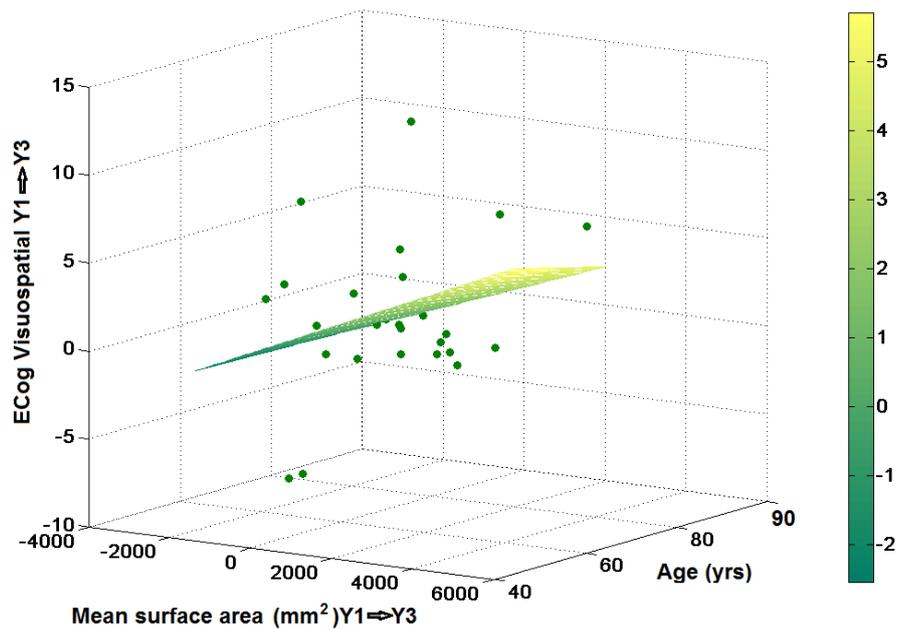


Figure 3. Plot of the results of the regression model that had the 2-year change in mean surface area and age as predictors and the change in the results of the ECog Visuospatial test in the same period as outcome variable.

The results of the exploratory analysis to evaluate the associations between changes in the general atrophy measurements (total CSV and ventricular size) and the changes in the outcome of the cognitive tests are shown in Table 2, and were obtained from the script General_atrophy_related_stats.m.

Table 2. Results from the exploratory analysis (i.e. using step-wise general linear modelling) of the associations between changes in the general atrophy measurements and the changes in the outcome of the cognitive tests.

General linear model			Estimate (p-value)	Estimate (p-value)
Outcome variable	Predictors	Model fitness (p-value)	for change in total CSF volume (% in ICV)	for change in ventricular volume (% in ICV)

FAQ(Y1→Y2)	CSF(Y1→Y2), age, MMSE, yrs education, FH dementia, gender, EMRF, CVRF	6.43e-05**	-0.0406 (0.124)	n/a
FAQ(Y1→Y3)	CSF(Y1→Y3), BV(Y1→Y3), age, MMSE, yrs education, gender, EMRF, CVRF	2.88e-05**	-1.30 (0.0049)*	6.90 (0.104)
FAQ(Y2→Y3)	CSF(Y2→Y3), BV(Y2→Y3), age, MMSE, yrs education, gender, EMRF, CVRF	0.000431**	0.930 (0.020)*	-10.979 (0.0022)*
MoCA(Y1→Y2)	CSF(Y1→Y2), BV(Y1→Y2), MMSE, yrs education, FH dementia, gender, EMRF, CVRF	0.00126*	3.177 (0.009)*	-41.028 (0.019)*
MoCA(Y1→Y3)	age, MMSE, yrs education, FH dementia, EMRF, CVRF	6.78e-05**	n/a	n/a
MoCA(Y2→Y3)	CSF(Y2→Y3), BV(Y2→Y3), age, MMSE, gender, EMRF, CVRF	8.37e-05**	-1.707 (0.0188)*	-1.871 (0.0748)
ECog Visuospatial (Y1→Y2)	age, MMSE, yrs education, FH dementia, gender	0.00225*	n/a	n/a
ECog Visuospatial (Y1→Y3)	CSF(Y1→Y3), age, MMSE, FH dementia, gender, EMRF	0.00187*	-1.131 (0.0054)*	n/a
ECog Visuospatial (Y2→Y3)	CSF(Y2→Y3), BV(Y2→Y3), age, MMSE, yrs education, CVRF	0.0554	1.358 (0.0333)*	-13.127 (0.0221)*

Legend: CSF = % cerebrospinal fluid volume in ICV, BV = % brain ventricular volume in ICV, MMSE = Mini Mental State Examination results at baseline, FH dementia = family history of dementia, EMRF = endocrino-metabolic risk factors, CVRF = cardiovascular risk factors, Y1 = year 1, Y2 = year 2, Y3 = year 3, n/a = not applicable due to term not included as predictor in the model.

Note: Past medical history of Cardiovascular Risk Factors refers to smoking, other risk factors mentioned in the participant's medical history, and previous medical reports of having (or not) any cardiovascular disease. The latter referred to/included the presence of coronary or peripheral artery disease, mild stroke, hypertensive or rheumatic heart disease, cardiomyopathy, carditis, heart arrhythmia, or thromboembolic disease. The most common risk factors described in the participant's medical history are hypertension and hypercholesterolaemia.

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