

# The Interplay Between Gray Matter and White Matter Neurodegeneration in Subjective Cognitive Decline

Nira Cedres (✉ [nira.cedres@ki.se](mailto:nira.cedres@ki.se))

Karolinska Institutet <https://orcid.org/0000-0002-1850-6451>

Patricia Diaz-Galvan

Karolinska Institute: Karolinska Institutet

Lucio Diaz-Flores

Hospital Universitario de Canarias

J-Sebastian Muehlboeck

Karolinska Institute: Karolinska Institutet

Yaiza Molina

Universidad Fernando Pessoa Canarias

Jose Barroso

University of La Laguna: Universidad de la Laguna

Eric Westman

Karolinska Institute: Karolinska Institutet

Daniel Ferreira

Karolinska Institute: Karolinska Institutet

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## Research

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# Abstract

**AIMS:** To investigate the interplay between gray matter (GM) and white matter (WM) neurodegeneration in subjective cognitive decline (SCD), including thickness across the whole cortical mantle, hippocampal volume, and integrity across the whole WM.

**METHODS:** We included 225 cognitively unimpaired individuals from a community-based cohort, of whom 123 endorsed one or more subjective cognitive complaints. GM neurodegeneration was assessed through measures of cortical thickness across the whole mantle and hippocampal volume. WM neurodegeneration was assessed through measures of mean diffusivity (MD) across the whole WM skeleton. Mediation analysis and multiple linear regression were conducted to investigate the interplay between the measures of GM and WM neurodegeneration.

**RESULTS:** A higher number of complaints was associated with reduced hippocampal volume, cortical thinning in several frontal and temporal areas and the insula, and higher MD across the WM skeleton, with a tendency to spare the occipital lobe. SCD-related cortical thinning and increased MD were associated with each other and jointly contributed to the complaints, but the contribution of cortical thinning to SCD was stronger.

**CONCLUSIONS:** Neurodegeneration processes affecting the GM and WM seem to be associated with each other in SCD and include brain areas other than those typically targeted by Alzheimer's disease (AD). Our findings suggest that SCD may be a sensitive behavioral marker of heterogeneous brain pathologies in individuals recruited from the community.

## 1. Background

Multiple pathologies can co-exist in cognitively unimpaired individuals, causing neurodegeneration years before the onset of cognitive decline [1]. Increasing research is trying to ascertain whether individuals are able to subjectively detect such neurodegeneration, motivating the emergence of concepts like subjective cognitive decline (SCD), as a risk factor for dementia [2–4]. Several studies showed that SCD may be a harbinger of Alzheimer's disease (AD) [5–7]. However, the neuropathology underlying SCD is heterogeneous and community-based studies show that SCD can also be associated with cerebrovascular disease [8–10] or age-related tauopathy [11].

Neurodegeneration can be assessed *in vivo* with magnetic resonance imaging (MRI). Previous studies revealed macrostructural neurodegeneration in the brain gray matter (GM) of SCD individuals, but the analyses were often limited to areas typically affected in AD. These studies consistently found reduced volumes in the hippocampus and entorhinal cortex [12–14], and cortical thinning in medial temporal areas [15–17]. Other studies expanded these analyses to include the entire cortical mantle by investigating AD-like atrophy patterns [18, 19]. However, investigating AD-related brain areas or AD-like atrophy patterns may hinder the possibility to detect neurodegeneration related to non-AD pathologies in SCD. Some studies overcame this limitation by exploring the whole cortex using voxel-based

morphometry or vertex-wise analysis in SCD [20–27]. While some authors reported reduced GM volume or thickness in hippocampus, precuneus, cingulum and frontal cortex in SCD individuals compared with healthy controls [20, 26], other authors reported no differences [22, 23], or even increased GM volume in fusiform gyrus and occipital areas in SCD [24, 25]. In addition, all these studies operationalized SCD mostly based on memory complaints and had a strong focus on AD, therefore GM neurodegeneration associated to non-memory complaints is still poorly understood.

In addition, several SCD studies investigated neurodegeneration in the white matter (WM) by using diffusion tensor imaging (DTI). The scarce data available suggest neurodegeneration in several WM areas in SCD [20, 21, 28–31]. However, some other DTI studies reported no WM neurodegeneration in SCD [22, 32]. An important question that remains unanswered is how WM and GM neurodegeneration relate to each other during the SCD stage. This question is relevant in order to elucidate the earliest stages of overt neurodegeneration in individuals at risk of dementia. So far, this question has only been investigated in one previous study [21]. Hong et al. (2016) investigated 46 SCD patients, of which 19 had a high risk of progressing to AD and 27 had a low risk of progressing to AD based on age, *APOE* genotype, and cognitive performance. Using DTI, Hong et al. (2016) showed that SCD patients at a high risk of progressing to AD had greater neurodegeneration in frontotemporal WM areas, while no differences were found in cortical thickness.

The overall goal of the current study was to extend the previous research on GM and WM neurodegeneration in SCD. To do that, we (i) investigated cortical thickness across the whole mantle, hippocampal volume, and integrity across the whole WM skeleton, and (ii) studied the interplay between GM and WM neurodegeneration. SCD was operationalized through complaints in several cognitive domains, not only memory, in a large community-based cohort of 225 individuals. Since the age is a major contributor to GM neurodegeneration [33], WM neurodegeneration [34], and subjective cognitive complaints [9], we also investigated the role of age in this study.

## 2. Methods

### 2.1. Participants

A total of 225 individuals were selected from the GENIC cohort [35], a community-based study from the Canary Islands (Spain). Inclusion criteria for the current study were in accord with the basic SCD criteria published by the SCD initiative (SCD-I) working group [4]: (1) Normal cognitive performance in comprehensive neuropsychological assessment using pertinent clinical normative data (i.e., individuals did not fulfill cognitive criteria for mild cognitive impairment or dementia); (2) preserved activities of daily living and global cognition, operationalized as a Blessed Rating Dementia Scale (BRDS) [36] score  $\leq 4$ , a Functional Activity Questionnaire (FAQ) [37] score  $\leq 5$ , and a Mini-Mental State Examination (MMSE) [38] score  $\geq 24$ ; (3) No abnormal findings such as stroke, tumors, hippocampal sclerosis, etc., in MRI according to an experienced neuroradiologist; (4) no medical history of neurological or psychiatric disorders (including a diagnosis of major depression), systemic diseases or head trauma; and (5) no

history of substance abuse. We also required all participants to have MRI data available, including three-dimensional T1-weighted and diffusion tensor imaging (DTI) sequences (please see below). Participants' recruitment in the GENIC cohort was done through primary care health centers, advertisements in local schools, and relatives and acquaintances of the research staff, covering a representative sample in terms of age, sex, and education. Participation was completely voluntary and all the participants gave written informed consent approved by the local ethics committee.

## 2.2. Subjective cognitive complaints

Subjective complaints were assessed through a questionnaire described elsewhere [9]. Briefly, participants were asked about nine yes/no questions referred to cognitive changes in approximately the last six months and answers were coded as 0 (absence of complaint) or 1 (presence of complaint). Answers were summed up and the total of complaints was obtained ranging from 0 to 9. The nine questions covered complaints in memory, orientation, executive functions, face recognition, language production, language comprehension, word-finding, reading and writing.

## 2.3. Magnetic resonance imaging (MRI)

Participants were scanned using a 3.0T GE imaging system (General Electric, Milwaukee, WI, USA) located at the *Hospital Universitario de Canarias* in Tenerife, Spain. A three-dimensional T1-weighted Fast Spoiled Gradient Echo (FSPGR) sequence and a DTI sequence were acquired in sagittal and axial planes, respectively. The parameters were as follows, T1-weighted: repetition time/echo time/inversion time = 8.73/1.74/650 ms., field of view = 250 × 250 mm, matrix = 250 × 250 mm, flip angle = 12°, slice thickness = 1 mm; DTI: repetition time/echo time = 15000/≈72 ms., field of view = 256 × 256 mm, matrix = 128 × 128 mm, 31 directions, B value = 1000, flip angle = 90°, slice thickness = 2.4 mm. Full brain and skull coverage was required for the MRI datasets and detailed quality control was carried out on all the images according to previously published criteria [39].

The T1-weighted images were processed and analyzed with the FreeSurfer 6.0.0 image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). The hippocampal volume (left + right) was selected for this study, divided by the estimated total intracranial volume (TIV) to account for variability in head size [40]. Statistical analyses were also performed across the cortical mantle. DTI data were processed and analyzed with the FSL software (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), using the FDT and tract-based spatial statistics (TBSS) tools. The measure of mean diffusivity (MD) was selected for statistical analysis. MD is an early indicator of neurodegeneration and is more sensitive to changes during preclinical AD and SCD stages as compared with other diffusivity measures [41, 42]. Careful visual quality control was performed on all the output data obtained from FreeSurfer and FSL, and manual edits were done when appropriate. TheHiveDB was used for data management and processing in this study [43].

## 2.4. Statistical analysis

To address the aim of investigating the association between subjective cognitive complaints and cortical thickness across the whole cortical mantle, a vertex-wise analysis was performed using the FreeSurfer software. We also conducted a separate vertex-wise analysis for the age variable and compared the overlap between the cortical maps obtained for subjective cognitive complaints and age. A general linear model was fitted at each vertex using cortical thickness as the dependent variable and subjective cognitive complaints or age as the independent variables. Permutations-based non-parametric tests with 5000 iterations were used with a cluster-forming threshold of  $p \leq 0.01$  (two-sided) using the family wise error (FWE) correction for multiple comparisons ( $p \leq 0.05$ ). The smoothing kernel (full width at half maximum, FWHM) was equal to 10 mm. Cortical thickness values of statistically significant clusters associated with subjective complaints were transformed into individuals' native space for computation of within-clusters average thickness used in subsequent analyses (from here, referred to as 'average cortical thickness').

To address the aim of investigating the association between subjective cognitive complaints and hippocampal volume (TIV corrected), we computed the Pearson correlation between the two variables. We also computed the Pearson correlation between hippocampal volume (TIV corrected) and the age variable.

To address the aim of investigating the association between subjective cognitive complaints and integrity across the whole WM skeleton, a voxel-based analysis on the white matter skeleton was performed using the FSL software. We also conducted a separate voxel-based analysis for the age variable and compared the overlap between the skeleton maps obtained for subjective cognitive complaints and age. A general linear model was fitted at each voxel using MD as the dependent variable and subjective cognitive complaints or age as the independent variables. Permutation-based non-parametric testing with 5000 iterations was used followed by threshold-free cluster enhancement (TFCE) and the family-wise error (FWE) correction for multiple comparisons ( $p \leq 0.01$ , two-sided). MD values of statistically significant clusters associated with subjective complaints in individual's native space were used to compute within-clusters average MD values for subsequent analyses (from here, referred to as 'average MD').

To address the aim of investigating the interplay between GM neurodegeneration and WM neurodegeneration, we developed an approach based on mediation models and multiple linear regression as described below.

The only previous study investigating the association between GM neurodegeneration and WM neurodegeneration in SCD used partial correlation analyses [21]. However, correlation analyses are limited when it comes to fully understand the way in how GM and WM neurodegeneration have an effect on each other and their joint contribution towards subjective cognitive complaints. A strength of our study is that we extended that approach by using mediation analysis. The advantage of mediation analysis is the possibility to ascertain the unique and combined contribution of GM and WM neurodegeneration towards the complaints. Further, by testing complementary models it can be studied whether one of the neurodegeneration markers is the main driver of the contribution towards the complaints. We specifically

tested: (i) whether GM neurodegeneration mediates the association between WM neurodegeneration and subjective cognitive complaints; and (ii) whether WM neurodegeneration mediates the association between GM neurodegeneration and subjective cognitive complaints. Mediation analysis were conducted using the “Mediation” R package [44]. The TIV-corrected hippocampal volume (left + right), and the average cortical thickness and average MD of statistically significant clusters (see above) were used as the input data for mediation analysis. Mediation model 1 was set with subjective cognitive complaints as the dependent variable (Y), the average MD as the independent variable (X), and the average cortical thickness as the mediator (M) (Fig. 1a). Model 2 was set with subjective cognitive complaints as the dependent variable (Y), the average MD as the independent variable (X), and the TIV-corrected hippocampal volume as the mediator (M) (Fig. 1b). Model 3 was set with subjective cognitive complaints as the dependent variable (Y), the average cortical thickness as the independent variable (X), and the average MD as the mediator (M) (Fig. 1c). Model 4 was set with subjective cognitive complaints as the dependent variable (Y), the TIV-corrected hippocampal volume as the independent variable (X), and the average MD as the mediator (M) (Fig. 1d). The four mediation models were fitted with and without the age as a covariate in order to investigate the role of age in our analyses.

The three basic conditions of mediation analysis [45] were tested with simple and multiple linear regression models: (1) the significant association between the mediator and the independent variable; (2) the significant association between the independent variable and the dependent variable; and (3) the significant association between the mediator and the dependent variable when the independent variable is also included in the model. Mediation was based on the average direct effect (ADE), the average causal mediation effect (ACME), and the total effect. Briefly, the ADE represents the direct effect of the independent variable on subjective cognitive complaints, while the ACME represents the indirect effect of the independent variable on subjective cognitive complaints, through the mediator variable. The total effect represents the sum of the ACME and the ADE. When the ACME is statistically significant (in conjunction with a significant total effect) there is a mediation effect that can be of two types: full mediation, when the ACME is significant but the ADE is not significant; and partial mediation, when both the ACME and the ADE are significant [44]. The ACME and the ADE were calculated by using confidence intervals based on non-parametric bootstrap sampling (1000 simulations). We also calculated the magnitude of the mediation effect by dividing ACME by the total effect (Fig. 1).

In addition, we applied multiple linear regression to investigate the partial association of the average cortical thickness, hippocampal volume, the average MD, and age with subjective cognitive complaints. We used the backwards option with the best general lineal model - *bestglm* - method for variables exit.

A p-value  $\leq 0.05$  (two-tailed) was considered significant in all these analyses.

### 3. Results

Two hundred and twenty-five cognitively unimpaired participants (mean age 54.7 years, range from 35 to 77 years, 55% female) were included in the current study. A total of 123 participants reported between 1

and 6 complaints, whereas 102 participants reported no subjective cognitive complaints.

### 3.1. The association between GM neurodegeneration and subjective cognitive complaints

The vertex-wise analysis showed that a higher number of subjective cognitive complaints was significantly associated with reduced cortical thickness in 11 clusters including lateral and medial frontal areas and the insula of both hemispheres, and lateral temporal areas in the right hemisphere (Table 1, Fig. 2a). The vertex-wise analysis fitted for age showed that older age was significantly associated with reduced cortical thickness across the whole cortex with a tendency to spare the occipital lobe (Fig. 2a). Figure 2a shows the overlap between the cortical maps related to subjective cognitive complaints and the age. As it can be seen, most of the cortical areas related to subjective cognitive complaints were also related to age (Fig. 2a).

Table 1  
The association between subjective cognitive complaints and cortical thickness

Cluster #	Max <sup>1</sup>	Brain area <sup>2</sup>	Size (mm <sup>2</sup> )	MNIX	MNIY	MNIZ	p-value
<i>Left hemisphere</i>							
1	-6.493	Superior frontal	2287.9	-6.9	39.4	38.3	< 0.001
2	-4.613	Precentral	2077.6	-36.0	-11.7	50.1	< 0.001
3	-5.811	Pars opercularis	1209.5	-35.8	14.2	9.9	< 0.001
4	-3.536	Caudal middle frontal	605.1	-37.9	0.9	30.8	0.003
5	-4.634	Paracentral	413.8	-18.0	-32.9	43.2	0.032
<i>Right hemisphere</i>							
1	-5.400	Precentral	2537.1	52.5	-2.9	34.4	< 0.001
2	-4.052	Superior frontal	1152.3	12.8	4.5	40.1	< 0.001
3	-4.339	Superior temporal	1094.8	52.1	-11.0	-8.8	< 0.001
4	-3.984	Caudal middle frontal	728.8	26.9	-0.5	41.9	< 0.001
5	-4.089	Superior frontal	722.1	23.0	4.6	57.5	< 0.001
6	-4.469	Pars triangularis	634.9	45.6	35.4	-5.8	0.002

<sup>1</sup>The Max indicates the maximum log<sub>10</sub>(p) value across the vertices in the cluster. <sup>2</sup>Location of the peak voxel as per the Desikan atlas in FreeSurfer. The MNI ordinates indicate the location of the peak vertex. P-values are cluster-wise.

The Pearson correlation for the association between the complaints and hippocampal volume showed that a higher number of subjective cognitive complaints was significantly associated with reduced hippocampal volume (Table 2). The Pearson correlation for the association between age and hippocampal volume showed that older age was significantly associated with reduced hippocampal volume (Table 2).

Table 2  
Correlation matrix for the average MD in significant clusters, average cortical thickness in significant clusters, age, and complaints.

	SCC	Age	Average MD
Age	0.37***	-	-
Average MD	0.36***	0.55***	-
Average cortical thickness	-0.49***	-0.60***	-0.47***
Hippocampal volume	-0.14*	-0.29***	-0.40***
SCC: subjective cognitive complaints; MD: mean diffusivity; ***p < 0,001; *p < 0.05.			

### 3.2. The association between WM neurodegeneration and subjective cognitive complaints

The voxel-based TBSS analysis showed that a higher number of subjective cognitive complaints was significantly associated with a higher MD in one large cluster involving most of the WM skeleton, with a tendency to spare the occipital lobe (Fig. 2b). The voxel-based TBSS analysis fitted for the age showed that an older age was significantly associated with higher MD in one large cluster involving most of the WM skeleton, with a tendency to spare the occipital and parietal lobes, as well as to spare tracts going through the internal capsule (Fig. 2b). The overlap between the cortical maps related to subjective cognitive complaints and the age shows that a higher MD in the internal capsule and posterior white matter tracts (i.e., splenium of the corpus callosum, posterior portion of the superior longitudinal fasciculus, posterior thalamic radiation, and forceps major) is exclusively associated with complaints (Fig. 2b).

### 3.3. The interplay between GM neurodegeneration and WM neurodegeneration related to subjective cognitive complaints.

The average cortical thickness, hippocampal volume, and average MD of the statistically significant clusters reported above were used as the input data for mediation analysis.

The average MD was significantly correlated with the average cortical thickness (condition 1 of mediation analysis, Fig. 1a and 1c, Table 2), indicating that a higher MD was associated with thinner cortex. The average MD was also significantly correlated with the hippocampal volume (condition 1 of mediation

analysis, Fig. 1b and 1d, Table 2), indicating that a higher MD was associated with a smaller hippocampal volume. Consistent with the voxel-based TBSS analysis, the test for condition 2 of the mediation analysis (Figs. 1a and 1b) showed that the average MD was significantly correlated with the complaints, indicating that a higher MD was associated with a higher number of subjective cognitive complaints (Table 2). Likewise, the average cortical thickness and hippocampal volume were significantly correlated with the complaints, indicating that cortical thinning and reduced hippocampal volume were associated with a higher number of subjective cognitive complaints (condition 2 of mediation analysis, Figs. 1c and 1d, Table 2).

Mediation analysis showed that the average cortical thickness partially mediated the association between the average MD and subjective cognitive complaints (mediation model 1, Fig. 1a). The age was not a significant covariate in this model. Further, hippocampal volume was not a significant mediator of the association between the average MD and subjective cognitive complaints (model 2, Fig. 1b). The average MD partially mediated the association between the average cortical thickness and subjective cognitive complaints (model 3, Fig. 1c). The age was not a significant covariate in this model. Finally, the total effect in model 4 was not significant (Fig. 1d), meaning that this model was completely driven by the association between average MD and subjective cognitive complaints.

The multiple linear regression model was significant ( $F_{(1, 222)} = 39.7$ ;  $p < 0.001$ ,  $R^2 = 0.263$ ). Congruent with the mediation analyses, complaints were mainly predicted by the average cortical thickness ( $\beta = -0.417$ ;  $p < 0.001$ ) and the average MD ( $\beta = 0.163$ ;  $p = 0.01$ ). Hippocampal volume ( $\beta = 0.063$ ;  $p = 0.322$ ) and age ( $\beta = 0.058$ ;  $p = 0.459$ ) were not significant predictors of the complaints in this multiple linear regression model.

## 4. Discussion

We investigated the interplay between GM and WM neurodegeneration in SCD, including thickness across the whole cortical mantle, hippocampal volume, and integrity across the whole WM skeleton. We found that the association between WM neurodegeneration and the complaints was widespread across the WM skeleton, with a tendency to spare the occipital lobe. In contrast, the association between GM neurodegeneration and the complaints was limited to frontal areas, the insula, and some temporal areas, including the hippocampus. Our analyses showed that GM and WM neurodegeneration were associated with each other and both contributed similarly to the complaints, although the contribution of GM neurodegeneration (cortical thickness) was stronger as illustrated by a greater mediation effect and a higher beta value.

In the current study, subjective cognitive complaints were associated with cortical thinning in bilateral frontal and right lateral superior temporal areas, as well as in the insula. We also found a significant association between complaints and hippocampal volume. However, there were no associations with other areas typically involved in AD, such as the entorhinal cortex and inferior parietal gyrus. This contrasts with previous studies on SCD, which reported a significant association between complaints and cortical thinning in the inferior parietal, inferior temporal, and middle temporal areas [14–16, 46, 47]. This

discrepancy could be explained by the fact that most of the previous SCD studies had a strong focus on AD: they included patients from memory clinics, operationalized SCD mostly based on memory complaints, and constrained their analysis to brain areas typically affected in AD [7, 12, 51, 13–15, 46–50]. In contrast, our cohort is community-based, we operationalized SCD using complaints in cognitive domains beyond memory, and analyzed the whole cortical mantle. In concordance with our results, a previous study analyzing the whole cortical mantle showed that SCD individuals had a widespread pattern of cortical thinning involving frontal, temporal, and parietal areas [20]. Altogether, these findings highlight that SCD is a heterogeneous entity where cortical thinning might be determined by multiple factors. One of the most prominent determinants of subjective cognitive complaints in community-based samples is older age [9, 52]. Our findings showed that older age was associated with GM neurodegeneration in most of the cortex, including most of the areas that were associated with the complaints. Interestingly, the only area associated with SCD that was not associated with age was the right lateral temporal area. Recently, Lim et al. [26] showed that, the only structural difference between SCD individuals who progressed to MCI/dementia over 5 years and those who remained stable was cortical thinning in right lateral temporal areas. These findings highlight the need to take multiple cortical areas into consideration to gain a better understanding of neurobiological processes underlying SCD in heterogeneous populations.

In addition, we found that subjective cognitive complaints were associated with worse WM integrity in widespread areas, clearly exceeding the areas associated with GM neurodegeneration. In particular, we observed that a higher number of cognitive complaints was associated with increased MD in most of the WM skeleton, with a tendency to spare the occipital lobe. A recent study also reported widespread WM degeneration in SCD [20]. Similar to the findings for GM neurodegeneration, we found that age was associated with WM neurodegeneration. Interestingly, the association between subjective cognitive complaints and WM neurodegeneration exceeded the effect of age in posterior brain areas and internal capsule, while the age was primarily associated with WM neurodegeneration in anterior brain areas, in our study. Age-related WM neurodegeneration has been primarily associated to changes in anterior WM tracts [53]. On the contrary, posterior WM tracts and the internal capsule are relatively spared in normal aging [34, 53], but they are prone to brain pathologies such as cerebrovascular disease and/or cerebral amyloid angiopathy (CAA) [54, 55]. Further, patients with dementia with Lewy bodies have worse WM integrity in posterior tracts like the ones identified in our current study [56]. In addition, AD patients with prominent cortical atrophy (i.e., the hippocampal-sparing subtype of AD) are prone to have WM lesions in posterior brain areas [57]. The internal capsule is an area especially vulnerable to microvascular damage [58]. Both the internal capsule and posterior WM tracts receive dense cholinergic input, and increased MD in cholinergic WM pathways was associated with greater cerebrovascular disease and lower cognitive performance in our cohort [59]. Our current study provides novel data on age-dependent and age-independent contributions to neurodegeneration and SCD in a community-based cohort. Investigating how pathologies such as amyloid-beta, tau, and, cerebrovascular disease contribute to the neurodegeneration in posterior brain areas in SCD is an interesting prospect for future studies.

Another novel contribution of the current study is the analysis on the interplay between GM neurodegeneration and WM neurodegeneration. To our knowledge, only one previous study has investigated the association between GM neurodegeneration and WM neurodegeneration in SCD [21]. Hong et al. (2016) included a small cohort of 46 SCD patients with memory complaints, of whom 41% had a high risk of progressing to AD based on the age, *APOE* genotype, and cognitive performance of their SCD patients. They assessed neurodegeneration in WM areas adjacent to the cortex using a ROI-based approach on DTI data. The authors reported that SCD patients at a high risk of progressing to AD had greater neurodegeneration in WM areas adjacent to frontotemporal and supramarginal cortices, and they did not find any differences in GM neurodegeneration [21]. Further, they demonstrated associations between several WM ROIs and an estimation of the average thickness across the whole cortical mantle. Our current study extends that approach by including a more fine-grained analysis of WM neurodegeneration at the voxel level, and we studied the association between GM neurodegeneration and WM neurodegeneration in areas exclusively associated with subjective cognitive complaints. We also extended the approach based on partial correlations in Hong et al. (2016) by applying mediation and multiple linear regression models, which provide richer information on the inter-relationship among variables. We found that cortical thickness and MD are strongly associated with each other and both jointly contribute to subjective cognitive complaints. However, the magnitude of the mediation and the beta value of cortical thickness were the highest, suggesting that GM neurodegeneration has a stronger contribution to SCD as compared with the contribution of WM neurodegeneration. In prodromal AD, GM neurodegeneration seems to be downstream to WM neurodegeneration in longitudinal studies [60]. In cross-sectional studies, this finding may be reflected by a stronger association between GM neurodegeneration and cognition and a weaker association between WM neurodegeneration and cognition [61]. Hence, our current findings could be interpreted as WM neurodegeneration preceding GM neurodegeneration during the stage of SCD. Further, we observed that WM neurodegeneration was widespread across the WM skeleton and GM neurodegeneration was limited to frontotemporal areas. Despite our WM marker is a microstructural measure and our GM marker is a macrostructural measure, this finding could also suggest a more advanced neurodegenerative process in the WM than in the GM, taking place during the SCD stage. Altogether, these data suggest that WM neurodegeneration might start earlier than GM neurodegeneration, and SCD seems to be a sensitive behavioral marker of heterogeneous processes of neurodegeneration.

## 5. Limitations

Some limitations should be noted. Although we report novel data on the interplay between GM neurodegeneration and WM neurodegeneration in SCD, the interpretation of WM neurodegeneration possibly preceding GM neurodegeneration needs to be confirmed in longitudinal studies. Follow-up data is being collected in the GENIC cohort to address this question in the future. Our current analyses showed an association of complaints with GM and WM neurodegeneration in brain areas other than those typically targeted by AD, which may suggest the contribution of non-AD pathologies. Because multiple pathologies usually coexist in the brain of cognitively unimpaired individuals [62, 63], future studies

should thus unveil the pathologies underlying non-AD patterns of GM and WM neurodegeneration in SCD. Investigating pathologies such as cerebrovascular disease and tauopathies is warranted due to their contribution to SCD in community-based cohorts [60, 63, 11, 64]. A limitation of our cohort is that we do not have biomarkers for amyloid-beta and tau-related pathologies.

## 6. Conclusions

This study is one of the few in investigating the association between GM and WM neurodegeneration in SCD. Our data suggest an association between neurodegeneration processes affecting the GM and WM in SCD individuals. However, GM neurodegeneration seemed to have a stronger contribution to SCD in our community-based cohort, highlighting brain areas that are typically not targeted by AD. This finding suggests the contribution of non-AD pathologies to SCD, and encourages that future studies extend imaging analysis to brain areas other than those typically involved in AD.

## Abbreviations

ACME: average causal mediation effect

AD: Alzheimer's disease

ADE: average direct effect

BDRS: Blessed dementia rating scale

CAA: cerebral amyloid angiopathy

DTI: diffusion tensor imaging

FAQ: Functional activity questionnaire

FSPGR: Fast Spoiled Gradient Echo

FWE: family wise error

FWHM: full width at half maximum

GE: General Electric

GM: gray matter

MD: mean diffusivity

MMSE: Mini mental state examination

MRI: magnetic resonance imaging

SCD: subjective cognitive complaints

TBSS: tract-based spatial statistics

TIV: total intracranial volume

WM: white matter

## 7. Declarations

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### Ethics approval and consent to participate

Participation was completely voluntary, and all the participants gave written informed consent approved by the local ethics committee.

### Consent for publication

Not applicable

### Availability of data and materials

The dataset generated and analyzed for the current study are available to qualified researchers upon reasonable request to the contact person Dr. Daniel Ferreira, [daniel.ferreira.padilla@ki.se](mailto:daniel.ferreira.padilla@ki.se).

### Competing interests

None

### Authors' contributions

NC, JB, EW, and DF contributed to the conception and design of the study. NC, PDG, YM, LDF, JSM, JB, EW, and DF contributed to the acquisition and analysis of data. NC, PDG, and DF contributed to drafting

significant portions of the manuscript and preparing the figures. All the authors revised the manuscript and contributed to scientific content.

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## Authors' information

<sup>a</sup>Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, 14152 Stockholm, Sweden ; <sup>b</sup>Hospital Universitario de Canarias, La Laguna, Tenerife, Spain; <sup>c</sup> Faculty of Health Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain; <sup>d</sup> Faculty of Psychology, University of La Laguna, 38205 La Laguna, Tenerife (Spain) <sup>e</sup> Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK;).

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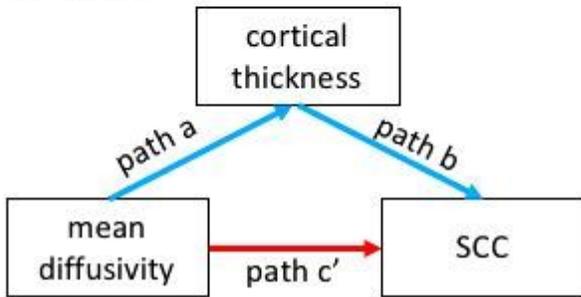
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## Figures

**Mediator: GM neurodegeneration**

**a) Model 1**



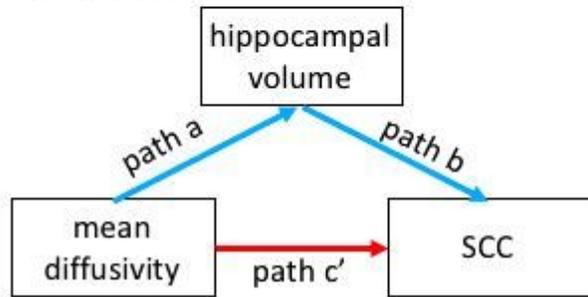
**ACME** (a+b) = 0.079\*\*\*

**ADE(c')** = 0.067\*\*

total effect = 0.147\*\*\*

Magnitude of mediation effect 53.7%

**b) Model 2**



**ACME** (a+b) = -0.003

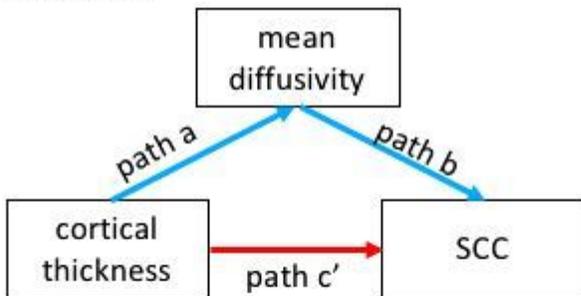
**ADE(c')** = 0.091\*\*\*

total effect = 0.087\*\*\*

No mediation

**Mediator: WM neurodegeneration**

**c) Model 3**



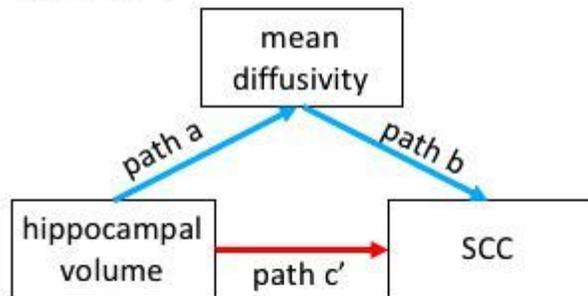
**ACME** (a+b) = -0.680\*\*\*

**ADE(c')** = -3.770\*\*\*

total effect = -4.450\*

Magnitude of mediation effect 15.3%

**d) Model 4**



**ACME** (a+b) = -112.731\*\*

**ADE(c')** = 49.122

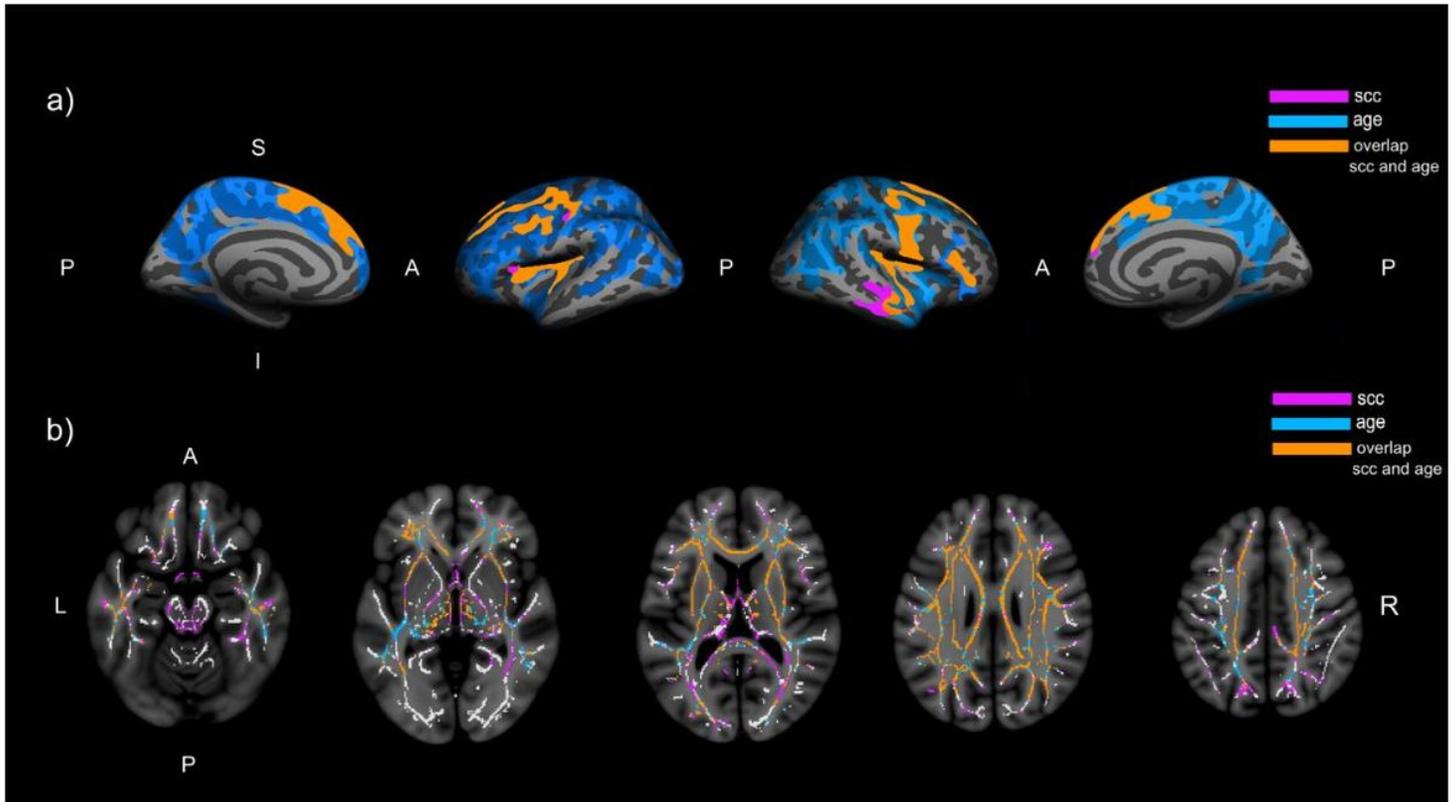
total effect = -63.609

No mediation

**Figure 1**

Mediation analysis. Panel (a) represents mediation model 1: subjective cognitive complaints as the dependent variable (Y), the average MD as the independent variable (X), and the average cortical thickness as the mediator (M); Panel (b) represents mediation model 2: subjective cognitive complaints as the dependent variable (Y), the average MD as the independent variable (X), and the TIV-corrected hippocampal volume (left+right) as the mediator (M). Panel (c) represents mediation model 3: subjective

cognitive complaints as the dependent variable (Y), cortical thickness as the independent variable (X), and the average MD as the mediator (M); Panel (d) represents mediation model 4: subjective cognitive complaints as the dependent variable (Y), the TIV-corrected hippocampal volume (left+right) as the independent variable (X), and the average MD as the mediator (M). Note: age was not a significant covariate in models 1 and 3. SCC: subjective cognitive complaints; ACME: average causal mediation effect; ADE: average direct effect; M: mediator; Magnitude of the mediation effect: ACME / total effect; X: independent variable; Y: dependent variable. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .



**Figure 2**

Association of subjective cognitive complaints and age with cortical thickness and white matter integrity. Panel (a) represents the cortical thinning exclusively associated with subjective cognitive complaints (pink), the cortical thinning exclusively associated with age (blue), and the cortical thinning associated with both complaints and age (orange). Panel (b) represents the increase in mean diffusivity exclusively associated with subjective cognitive complaints (pink), the increase in mean diffusivity exclusively associated with age (blue), and the increase in mean diffusivity associated with both complaints and age (orange); The white matter skeleton is represented in white color. All the represented clusters are statistically significant at  $p > 0.01$  after correction for multiple testing; A: anterior; P: posterior; S: superior; I: inferior; L: left; R: right; SCC: subjective cognitive complaints