# Investigating Compensatory Brain Activity in Older Adults with Subjective Cognitive Decline

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### 23 Abstract.

- Background: Preclinical Alzheimer's disease (AD) is one possible cause of subjective cognitive decline (SCD). Normal
- task performance despite ongoing neurodegeneration is typically considered as neuronal compensation, which is reflected
   by greater neuronal activity. Compensatory brain activity has been observed in frontal as well as parietal regions in SCD, but
- data are scarce, especially outside the memory domain.
- **Objective:** To investigate potential compensatory activity in SCD. Such compensatory activity is particularly expected in
- <sup>29</sup> participants where blood-based biomarkers indicated amyloid positivity as this implies preclinical AD.
- Methods: 52 participants with SCD (mean age:  $71.00 \pm 5.70$ ) underwent structural and functional neuroimaging (fMRI), targeting episodic memory and spatial abilities, and a neuropsychological assessment. The estimation of amyloid positivity
- was based on plasma amyloid- $\beta$  and phosphorylated tau (pTau181) measures.
- **Results:** Our fMRI analyses of the spatial abilities task did not indicate compensation, with only three voxels exceeding an uncorrected threshold at p < 0.001. This finding was not replicated in a subset of 23 biomarker positive individuals.

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Conclusion: Our results do not provide conclusive evidence for compensatory brain activity in SCD. It is possible that neuronal compensation does not manifest at such an early stage as SCD. Alternatively, it is possible that our sample size was too small or that compensatory activity may be too heterogeneous to be detected by group-level statistics. Interventions based on the individual fMRI signal should therefore be explored.

Keywords: Blood-based biomarkers, episodic memory, functional MRI, neuronal compensation, spatial abilities, subjective
 cognitive decline

### 35 INTRODUCTION

Subjective cognitive decline (SCD) is defined as 36 self-perceived cognitive decline that does not man-37 ifest in cognitive tests and affects around 20% of 38 individuals older than 65 years [1]. SCD might have 39 different causes (e.g., neurodegenerative disorders, 40 psychiatric disorders, or head trauma) [2]. Despite 41 achieving normal results in neuropsychological tests, 42 the average performance in SCD is somewhat lower 43 in episodic memory measures of immediate and 44 delayed verbal recall, compared to healthy older 45 adults [3, 4]. Regardless of variations in the trajec-46 tory of SCD, it is considered an at-risk state for the 47 development of Alzheimer's disease (AD), particu-48 larly when the individual is worried about the decline. 49 Longitudinal studies show that SCD approximately 50 doubles the risk of developing manifest dementia 51 in the following years within five years [5]. This is 52 in line with several studies that reported increased 53 biomarkers of AD in SCD [6]. Studies investigat-54 ing amyloid- $\beta$  for example, reported greater levels 55 of amyloid depositions in positron emission tomog-56 raphy (PET) in participants with greater SCD [7, 57 8]. Therefore, increased amyloid levels might be 58 associated with SCD many years before cognitive 59 impairment manifests [6]. The recent development 60 of amyloid-B blood biomarkers allows the estimation 61 of PET amyloid positivity throughout the different 62 phases of the AD spectrum [9]. Tau depositions are 63 another biomarker of AD but also SCD [6]. pTau181 64 has been associated with amyloid and tau PET posi-65 tivity in healthy older adults and participants with AD 66 [10]. These blood-based biomarkers have the poten-67 tial to identify amyloid positive individuals, which 68 might be in a preclinical stage of AD (SCD likely 69 due to AD). 70

There seems to be a complex interaction between
brain activity, brain area and disease stage in cognitive impairment. In the memory domain, a recent
study in individuals with SCD, mild cognitive impairment (MCI) and healthy controls reported an inverse
quadratic relationship for task-related activation in

an associative memory task in the left parietal lobe across the different study samples. For the hippocampus and other brain regions a negative linear relationship described the activation better than the quadratic function in relation to the volume, i.e., activation was constantly greater when volume became lower. The SCD classification included APOE genotyping (ɛ4 carrier) and/or biomarker evidence (left or right hippocampal volume one standard deviation below the mean of the healthy control sample) to increase the likelihood of including participants with preclinical AD [11]. In another study, hyperactivity in the hippocampus at baseline predicted increased longitudinal amyloid deposition, which was not the case for cortical regions. This indicates that hippocampal hyperactivity is related to pathological effects, while greater cortical activity reflects compensatory processes [12]. Evidence for compensatory activity in SCD has also been found outside the parietal cortex. In individuals with subjective memory complaints, the right dorsolateral prefrontal cortex showed greater activity during cued recall in a face-occupation task, while task performance in this sample was not significantly different from healthy controls. The face-occupation task assesses associative episodic memory and especially the recall condition is a sensitive test for early memory impairment in the course of AD [13]. Another study reported greater prefrontal activity in participants with subjective memory decline in an episodic memory encoding task as an indicator of compensatory activity [14].

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In addition to the results from functional neuroimaging, two systematic reviews summarizing structural brain changes in SCD reported heterogeneous results. However, a lower hippocampal volume has been a consistent finding [6, 15]. The hippocampus is part of the medial temporal lobe (MTL), which is affected by neuropathology (e.g., atrophy) early in AD whereas neocortical structures like the parietal lobe are affected later [16]. Therefore, many imaging studies have focused on the MTL. The parietal lobe is less investigated in SCD even though it is prone to exhibit early amyloid deposition [17, 18]. Both

the MTL as well as the parietal lobe are relevant in episodic memory [19–22].

In the spatial domain, impairments are observed 122 early in the course of AD. Delayed recall performance 123 in visuospatial memory tasks like the delayed recall 124 in the Rey-Osterrieth complex figure test has shown 125 the ability to discriminate MCI from healthy aging 126 [23]. Spatial abilities include different subfunctions 127 like spatial perception and mental rotation [24]. A 128 meta-analysis reported consistent activity in the supe-129 rior and inferior parietal lobes in both hemispheres in 130 mental rotation and spatial imagery tasks in healthy 131 subjects [25]. While no study with functional mag-132 netic resonance imaging (fMRI) investigated spatial 133 abilities in SCD, greater activity in parietal and 134 temporal areas has been reported in MCI. As no 135 significant difference in task performance between 136 the MCI sample and healthy controls was found this 137 might indicate compensatory activity [26]. 138

Overall, there is evidence for compensatory activ-139 ity in SCD, but data is scarce. More data for 140 this population is especially important because 141 SCD allows the study of early compensatory brain 142 changes. But there exists no clear definition of how 143 neuronal compensation can be addressed. Gregory 144 et al. [27] defined a model to operationalize com-145 pensatory brain activity in neurodegeneration due to 146 Huntington's disease. This model includes three vari-147 ables: task performance, a proxy of disease severity, 148 and brain activity. In an early disease-stage accompa-149 nied by normal performance, compensation through 150 greater brain activity is possible. Generally, com-151 pensatory activity is seen in early or mild cases 152 of neurodegeneration. In later disease-stages perfor-153 mance starts to decline as disease severity increases 154 and compensation is no longer possible [27]. In accor-155 dance with previous studies, we hypothesized that 156 compensatory effects in SCD will be present in pari-157 etal [11] and/or frontal [13, 14] brain regions and 158 will be most pronounced in subjects with probable 159 amyloid positivity. 160

The aim of this study was to investigate the exis-161 tence of compensatory brain activity in SCD. As 162 a lower hippocampal volume was a stable finding 163 in studies investigating SCD, we used hippocampal 164 atrophy as an indicator of potential neurodegenera-165 tion associated with SCD. We deployed the model 166 of Gregory et al. [27] in fMRI tasks on episodic 167 memory and spatial abilities. We selected these tasks 168 based on their involvement of the parietal lobe and the 169 early impact of AD related pathologies on task per-170 formance. In the episodic memory task we focused 171

on the cued recall condition as this is a sensitive test for early memory impairment in AD [13]. We defined successful neuronal compensation as greater activity in brain regions correlated with greater task performance in the presence of high hippocampal atrophy. Hippocampal atrophy served as a marker of disease related neuropathology. Compensatory effects might be most pronounced in SCD if it is a preclinical state of AD. Therefore, we repeated the fMRI analyses in a subsample with probable amyloid positivity according to blood biomarkers for amyloid- $\beta$  or pTau.

METHODS

This bi-centric study (Bern and Lucerne; Switzerland) was approved by both local Ethics Committees and registered on ClinicalTrials.gov (NCT04452864). All study participants gave informed consent before the first study visit.

### Participants

52 Caucasian participants (mean age 71.00, SD: 5.70, mean years of education: 15.15, SD: 3.06) were included in the analyses. The data were collected as part of the baseline assessment of a cognitive training study [28]. This assessment was the first in person contact of the participants with a member of the research team, therefore, we do not assume any effect of the planned intervention or general study setting on the results. We included participants who reported subjective cognitive complaints and related worries as this increased the probability to include participants with SCD likely due to AD [2]. To identify SCD, participants completed a questionnaire on memory related concerns and attentional deficits during the last 12 months. Language or other cognitive abilities were not assessed. This questionnaire is based on suggested criteria for SCD [29]. We included participants only if they reported a decline in memory or attention functions and expressed related worries. For this categorical questionnaire no cut-off scores are available.

Other inclusion criteria were age between 60–85 years, native or fluent German speakers and normal or corrected to normal vision. Exclusion criteria included a diagnosis of cognitive impairment (MCI or dementia), a severe neurological or acute psychiatric disease, substance abuse, current psychoactive medication, contraindication for MRI (i.e., metal implants) or stroke in previous history. The diagnosis of MCI was based on established criteria [30]. Furthermore, 178 179 180

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participants which scored below 23 points in the 220 MoCA were excluded from this study as this is an 221 indicator of objective cognitive decline [31]. 222

For 21 participants no increased cardio-vascular 223 risk factors were identified (i.e., no self-reported high 224 blood pressure, cardiac disease, or abnormalities in 225 the MRI data). 18 participants reported high blood 226 pressure and 5 participants reported heart problems 227 (e.g., heart attack or auricular fibrillation in the past). 228 T1 weighted MRI images were investigated by a clin-229 ical neuroradiologist to rate hypointensities, which 230 could reflect a vascular component explaining cogni-231 tive impairment. 34 participants of our sample had a 232 Fazekas score (i.e., presence of white matter lesions) 233 [32] of 0, for 10 participants the score was 1, for 7 234 participants the score was 2 and for 1 participants 235 the score was 3. Of note, we did not acquire FLAIR 236 or similar sequences, which would have been more 237 sensitive measure of white matter lesions. 238

51 participants were included in the fMRI model 239 for the episodic memory fMRI task, one participant 240 was excluded due to motion artefacts.

Blood samples from 38 participants were available. 242 To investigate neuronal compensation specifically in 243 SCD likely due to AD, we repeated all analyses with a 244 subsample with blood biomarkers indicating amyloid 245 positivity (n = 23). In this subsample, one participant 246 had to be excluded from analyses in the episodic 247 memory fMRI task due to motion artefacts. 248

#### Neuropsychological assessment and behavioral 249 composite scores 250

The neuropsychological test battery included the 251 Montreal Cognitive Assessment (MoCA) [33], audi-252 tory verbal learning test (AVLT) [34], Rey–Osterrieth 253 complex figure (RCF) [32], flanker test [36], graded 254 naming test [37], semantic fluency, digit span for-255 ward and backward, and questionnaires related to the 256 cognitive training intervention. Additional question-257 naires assessed situational motivation [38], quality 258 of life [39], activities of daily living [40], handedness 259 [41] and depressive symptoms [42]. Furthermore, we 260 assessed subjective cognitive complaints in self and 261 informant rated versions. The MoCA was the only test 262 performed as paper-pencil version, all other tests and 263 the questionnaires were administered using a tablet 264 (iPad, 7. Generation) with the Apollo App [43]. 265

We computed a composite score of episodic mem-266 ory and spatial abilities based on raw test scores. 267 The episodic memory (memory) composite score 268 included the learning sum, immediate and delayed 269

recall of the AVLT. The spatial abilities composite score included encoding, immediate and delayed recall from the RCF. Before calculating the behavioral composite scores, two principal component analyses (PCAs) were performed, one for the three AVLT and the other for the RCF scores. In a next step, we centered and standardized the three test scores included in the composite score. If the PCA showed different loadings for the test scores (i.e., the differences between two loadings were larger than 0.05) within one composite score, the centered and standardized scores were weighted according to their loading and a mean score was calculated, resulting in one memory and one spatial abilities composite score.

### Blood-based biomarkers

We used the amyloid- $\beta_{42/40}$  (A $\beta_{42/40}$ ) ratio and pTau181 measures to identify participants with probable AD-specific neuropathologies and repeated the fMRI analyses with a subsample with positive blood biomarkers for amyloid positivity.

For blood biomarker measurement in this study we used N4PE Simoa immunoassays (IA-N4PE) developed by Amsterdam University Medical Center, Amsterdam, the Netherlands, and ADx Neurosciences, Ghent, Belgium, and commercially available from Quanterix, Billerica, Massachusetts [44]. Cut off scores of 0.06 for the A $\beta_{42/40}$  ratio and 1.8 pg/ml for pTau181were used. These are based on unpublished data in which 1111 participants with known amyloid status based on CSF or amyloid PET from the Amsterdam Dementia Cohort were analyzed (AUC for  $A\beta_{42/40}$  0.735 and for p-tau181 0.828).

### Study procedures

The duration of the study visit was approximately 3 h, including the MRI session. After signing the consent form, the MoCA and tablet-based cognitive tests were performed. Next, participants practiced all conditions of the fMRI tasks outside the MRI scanner to ensure task comprehension. The MRI session itself took around 50 min. The session started with a resting-state fMRI (rs-fMRI) while fixating a cross, followed by the face-occupation task (episodic memory) during task-based fMRI, T1 w structural imaging, a visual construction task targeting spatial abilities during task-based fMRI, and an arterial spin labelling (ASL) protocol. This listing of MRI sequences corresponds to the order in MRI

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data acquisition. Data on rs-fMRI and ASL are not reported here.

#### 320 Face-occupation task

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Episodic memory was assessed with a blocked face-occupation task (duration: 638 s, Fig. 1), which was based on a previous study [45]. This paradigm induces activity in the MTL and occipital brain areas [46]. Additionally, cued recall tasks have been suggested as sensitive markers for AD [13, 47] and have been related to CSF markers of AD [47].

The task included four conditions which were pre-328 sented in the same order (encoding, cued recall, 329 recognition, control condition) in six runs. Before 330 the encoding block a task instruction was shown 331 ("Please remember the people and their job. Does the 332 face fit to the job? Yes = 2, No =  $3^{\circ}$ ). This text disap-333 peared after 4s and the first of five face-occupation 334 associations was shown. Below the picture and the 335 occupation the question "Does the face fit to the job? 336 Yes = 2, No = 3" was displayed. The aim of this ques-337 tion was to induce a deeper level of encoding [13]. 338 This block was followed by the control condition. 339 The instruction text appeared again for 4s ("Sil-340 houettes: Male or female? 2 = Female, 3 = Male"). 341 This text was followed by five head contours with 342 the question "2 = Female/3 = Male" right aside. Then 343 the instruction for the cued recall condition was dis-344 played for 4s ("What is this person's education? 345 2 = University degree, 3 = Apprenticeship"). During 346 the cued recall condition, a previously learned face 347 appeared as cue with the text "2 = University degree/ 348 3 =Apprenticeship" right aside. For the recognition 349 condition the instruction was "What is this person's 350 occupation?". This instruction screen was followed 351 by the presentation of the five faces that had also been 352 shown during the encoding and cued recall condition. 353 The faces were shown with two occupations and the 354 correct one had to be selected by button press. One 355 block lasted 21.25 s and included one condition. The 356 given answer was indicated by the font color switch-357 ing from white to grey. The interstimulus-interval was 358 0.5 s and stimuli were displayed for 3.75 s, regardless 359 of the answer from the participant. After the third run 360 the 15 face-occupation associations were presented 361 again in the same order. This repetition was included 362 to limit the number of stimuli to remember. As stimuli 363 eight pictures of female and seven pictures of male 364 faces from the Ebner face database [48] were shown. 365

As performance measure, we computed task accuracy for cued recall and recognition blocks.

#### Spatial construction task

Spatial abilities were assessed with a blocked spatial construction task (duration: 604 s, Fig. 2). This task was designed in accordance with a task which has been shown to elicit bilateral activation in parietal and occipital brain regions [49]. Spatial abilities are another domain early affected by behavioral deficits in the course of AD [50].

The task included four conditions (translation and rotation and the respective control conditions, luminance translation and luminance rotation). Participants had to either translate or rotate geometric puzzle pieces mentally in order to decide if the pieces fit together to build a square. As control condition, participants indicated if the two grey squares in black boxes in similarly shaped puzzle pieces were of the same grayscale. The task included two runs with eight blocks each. Before each block an instruction text was displayed for 3 s (rotation/translation conditions: "Do these shapes build a square? 2 =Yes, 3 =No"; luminance conditions: "Are the squares displayed in the same opacity? 2 = Same, 3 = Different''). One block lasted 24 s and included one condition. During the block the text "2 =Yes, 3 =No" or "2 =Same, 3 = Different" was displayed below the puzzle pieces. Each block was presented four times in a fixed order ensuring that translation and rotation conditions would always alternate. Between two blocks, breaks of 12 s and of 27 s between two runs were included during which a black fixation cross was displayed. In the long break (27 s), a text was displayed that now is a short break and the participant should not move. During the task each stimulus was presented for 2.5 s if no button press occurred. After button press or 2.5 s, the stimuli disappeared and a fixation cross appeared for 0.4 s. Stimuli within a block were displayed in a randomized order. Due to the fixed block duration in combination with self-paced trial solving, the number of solved trials differed between participants.

Performance was computed analogous to the episodic memory task but here the translation and rotation condition were combined to obtain one value for spatial abilities task accuracy. Due to the fixed block length, the presentation duration of the last trial of each block varied. Therefore, the last trial of each block was not included in the analysis.

Participants answered with the index (2/yes/ female/same) and middle finger (3/no/ male/different) of the right hand, using a Celeritas® button box with two buttons. Left-handers were asked to use the right-hand.

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Fig. 1. Face-occupation task. A) Encoding: participants were asked whether a face matches an occupation (subjective rating) B) Control condition: participants were asked to indicate whether a male or female silhouette is shown. C) Cued recall: a face from the encoding condition was presented as cue and participants indicated whether the occupation of the presented person requires a university degree or an apprenticeship. D) Recognition: participants had to choose the correct job between two different options.



Fig. 2. Spatial construction task. A) Translation and C) Rotation conditions: participants had to either translate or rotate puzzle pieces mentally in order to decide if the pieces fit together to build a square. As control condition, participants indicated if the two grey squares in black boxes in similarly shaped puzzle pieces were of the same grayscale (B) Luminance translation and D) Luminance rotation condition).

### 419 MRI data acquisition

Neuroimaging was acquired with a 3T Siemens 420 scanner (Bern: Siemens Magnetom Prisma, 32 chan-421 nel head coil; Lucerne: Siemens Magneton Vida, 64 422 channel head coil). Sequences and coil system at the 423 Lucerne site were adapted to resemble the protocol in 424 Bern to acquire high quality data while minimizing 425 hardware differences (please see statistical analy-426 ses section for the handling of site differences). The 427 described MRI parameters below were identical at 428 both study sites. 429

From all participants, T1- weighted images 430 TR = 5000 ms, $TE = 2.98 \, ms$ , (MP2RAGE, ΤI 431 1/2 = 700 ms/2500 ms,flip angle  $1/2 = 4^{\circ}/5^{\circ}$ . 432 FOV = 256 mm x 256 mm, matrix = 256 x 256, voxel 433 size =  $1 \times 1 \times 1$  mm, 176 slices) were acquired. 434

For the fMRI sequences we used echo-planar 435 imaging (EPI) with 604 (spatial abilities Task) and 436 638 (episodic memory task) volumes (TR = 1000 ms, 437 TE = 37 ms, flip angle = 30°, FOV = 230 mm x 438 230 mm, matrix =  $92 \times 92$ , accelerating factor 8, voxel 439 size 2.5 x 2.5 x 2.5 mm, 72 slices). The axial slices 440 were positioned along the anterior commissure and 441 the posterior commissure. 442

### 443 MRI processing

To calculate hippocampal atrophy, the struc-444 tural images were automatically segmented with 445 the computational anatomy toolbox (CAT12: 446 http://www.neuro.uni-jena.de/cat/). ROIs were 447 calculated using the neuromorphometrics atlas. To 448 calculate hippocampal atrophy, total hippocampal 449 volume was scaled by total intracranial volume 450 and the results subtracted from one, so that larger 451 numbers were corresponding to higher levels of 452 hippocampal atrophy. 453

To provide a grey matter mask for the task fMRI 454 group analyses, the anatomical images of each partic-455 ipant were segmented using SPM12 [51] in MATLAB 456 version 2019b (Natick, MA: The MathWorks Inc.) on 457 a Linux platform. After segmentation the individual 458 grey matter images were spatially normalized to stan-459 dard MNI space and then combined into one mean 460 image over all participants as grey matter mask. 461

Functional volumes were first realigned to the
mean image of each individual, coregistered to
the anatomical image in native space and finally
smoothed with a 6 mm full width at half maximum
Gaussian Kernel.

As first-level analyses general linear models were computed for each participant in native space with BOLD signal changes as dependent variable. Each block type was included as separate predictors with one additional predictor for instruction screens and breaks (episodic memory task: encoding, control, cued recall, recognition, instruction screens; spatial abilities task: translation, rotation, luminance translation, luminance rotation, instruction screens). To account for possible head movements, the absolute values of the first derivate of the six default movement parameters obtained during realignment were included. Each predictor's time course was convolved with a standard hemodynamic response function. A 128-s high pass filter was used to account for scanner drift and a separate variable was added to model the intercept. The resulting first level contrast images were then normalized into MNI space and resampled to isometric voxels with a side length of 2 mm.

To test if severe motion artefacts were present in the fMRI data, the absolute derivate of the first three movement parameters (x, y, z axis) were checked for values exceeding 2 mm between subsequent volumes. Two participants exceeded this threshold in the episodic memory task, one participant 17 times and one participant once. The participant with 17 movements was excluded from data analysis in the face-occupation episodic memory task. In the spatial abilities task, movements exceeding 2 mm were observed once in one participant and, therefore, no participants were excluded.

### Statistical analyses

### Behavioral data analyses

To investigate the association between blood-based biomarkers, behavioral composite scores and hippocampal atrophy we performed correlation analyses as well as partial Pearson's correlation analyses controlling for age. For categorical variables (APOE  $\varepsilon$ 4 carrier: yes/no) Welch's t-tests were used. We also used Welch's t-tests to test for significant differences between study sites in behavioral composite scores, hippocampal atrophy, and fMRI task accuracy. Paired t-tests were used to investigate differences in task accuracy, reaction times and number of solved trials between the different conditions in the fMRI tasks.

The analysis of the behavioral data was performed with R studio [52].

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### 516 Imaging data analyses

Spatially normalized contrast images from the 517 individual subjects level coding cued recall > control 518 contrasts (i.e., deciding if the occupation associated 519 with the presented face requires an apprentice-520 ship or university degree>is the presented head 521 contour male or female) from the face-occupation 522 episodic memory task entered group level analyses 523 (second level). We expected this contrast to elicit 524 parietal activity associated with episodic memory 525 retrieval processes. A study using a similar face-526 name paradigm for example, reported activation 527 during successful retrieval in the posteromedial cor-528 tex compared to lower activation during encoding 529 in young adults [53]. Furthermore, cued recall tasks 530 are sensitive markers for early AD related memory 531 impairment [13, 47] 532

For the visual construction task, we selected the [translation+rotation]>[luminance translation+luminance rotation] contrast, in accordance with the results of Seydell et al. [49] which showed strong parietal activity.

As outlined in the introduction, patterns reflecting neuronal compensation were defined as regions where greater functional activity is associated with greater hippocampal atrophy and better task performance [27].

To investigate potential neuronal compensation, 543 we used inclusive masking with an orthogonal (i.e., 544 independent) contrast as in previous work [54]. 545 In detail, significant activity with an uncorrected 546 threshold of p < 0.01 in a first t-contrast for activity 547 correlating with hippocampal atrophy was calculated. 548 The resulting image was used as inclusive binary 549 mask for a second estimation of the same contrast 550 with activity positively correlated with fMRI task 551 performance. For this second contrast estimation a 552 family-wise error correction (FWE, p < 0.05) for mul-553 tiple testing as well as a less conservative threshold of 554 p < 0.001 uncorrected were used. The masking image 555 included only few clusters where activity could be 556 detected in the second contrast. Therefore, p-values in 557 the second contrast estimation were corrected for the 558 small search region with a small volume correction 559 after masking. 560

While we selected tasks especially activating parietal areas, compensatory brain activity might also appear in brain areas outside the parietal lobe. Therefore, we performed whole brain analyses with the grey matter mask calculated for the study sample (please see below for detailed information about the grey matter mask). We included the fMRI in-task performance measures in the main models (model 1.1: Compensation related to performance in the episodic fMRI task; model 2.1: Compensation related to performance in the spatial abilities fMRI task). In a secondary analysis, we included performance measures from the behavioral composite scores instead of fMRI task performance, these models are reported in the Supplementary Material (model 1.2: Compensation related to the memory composite score; model 2.2: Compensation related to the spatial abilities composite score).

As previously mentioned, we repeated all analyses with a subsample with positive blood biomarkers for amyloid positivity (model 1.3: Compensation related to performance in the episodic memory fMRI task in a subsample with positive blood biomarkers for amyloid positivity; model 2.3: Compensation related to performance in the spatial abilities fMRI task in a subsample with positive blood biomarkers for amyloid positivity). The results from the subsample whole brain analyses and the detailed results from the models including fMRI task performance are reported in the Supplementary Material (model 1.4: Compensation related to performance in the memory composite score in a subsample with positive blood biomarkers for amyloid positivity; model 2.4: Compensation related to the spatial abilities composite score in a subsample with positive blood biomarkers for amyloid positivity). We did not correct for the number of models as we aimed to detect indications for compensation and consequently employed liberal statistical thresholds throughout (i.e., p < 0.01for the masking image and pFWE < 0.05 as well as puncorrected < 0.001 for the combination of both contrast images) [55]. For the same reason, we did not apply a voxel extent threshold. In all models one-sample t-tests were performed. Another possibility to investigate neuronal compensation is to build two samples according to the residuals in a linear regression for task performance and hippocampal atrophy. Participants with positive residuals in the regression scored better than estimated based on their hippocampal volume and we expect neuronal compensation to be most likely in this group (i.e., sample one). This is not the case in participants with null or negative residuals (i.e., sample two). We compared these samples with two-sample t-tests. Furthermore, we performed two-sample t-tests to compare subsamples with and without probable amyloid positivity based on blood biomarkers. The results for these analyses are reported in the Supplementary Material.

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Demographics of participants Mean SD Range 71 5.70 60-81 Age (y) Gender (m/f) 22/30 Education (y) 15.15 3.06 9-20 MoCA Score 27.32 1.97 24 - 30Composite Score M 0.00 0.93 -2.29 - 1.6

Table 1

SD, standard deviation; M, memory; SA, spatial abilities.

Composite Score SA

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All reported p-values in the fMRI analyses correspond to the peak-level significance and coordinates to the MNI space (x, y, z).

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-1.20-0.93

Age was related to hippocampal atrophy and 623 behavioral performance (please see the section "Rela-624 tionship between behavioral data and hippocampal 625 atrophy" for the results of the correlation analyses) 626 and, therefore, was included as covariate in all fMRI 627 analyses. Because MRI devices and head coils were 628 different between study sites, site was also included as 620 covariate. Sex was not related to hippocampal atrophy 630 or behavioral composite scores (please see Table 3 631 for detailed results), but to address potential neuronal 632 differences between females and males [56], sex was 633 included as additional covariate. 634

### 635 **RESULTS**

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Demographic details for the participants are summarized in Table 1. The mean score of the geriatric depression scale [42] was 1.73 (SD: 1.55). No participant had ten or more points, which would indicate severe depressive symptoms.

The mean values and standard deviations of the six test scores included in the behavioral composite scores are reported in the Supplementary Material.

To explore potential effects of study site on behav-644 ioral outcomes and hippocampal atrophy scores 645 Welch's t-tests were performed for the behavioral 646 composite scores (memory: t(35.68) = -1.97, p = 0.06; 647 spatial abilities: t(31.95) = -0.1, p = 0.91), hippocam-648 pal atrophy (t(46.59), p = 0.50) and fMRI task 649 accuracy (memory: t(23.71), p=0.72; spatial abili-650 ties: t(32.13), p = 0.93). The results did not indicate 651 significant differences between study sites in any of 652 these outcomes. Therefore, the correlation analyses 653 were not controlled for study site. 654

### 655 Composite scores

For the episodic memory outcomes, the PCA showed very similar loadings (loading AVLT delayed recall: -0.58, loading immediate recall: -0.57, loading total learning sum -0.58). Therefore, no weighting of the single raw test scores was performed for the behavioral composite score. The PCA for the SA raw scores showed differences between the loadings of the encoding and the two other scores which were larger than 0.05 (loading RCF encoding; -0.41, loading immediate recall: -0.65, loading delayed recall: -0.6). Therefore, we weighted the individual test scores with their absolute loads before combining them into one composite score.

### Relationship between behavioral data and hippocampal atrophy

There was a significant correlation between performance in measures of episodic memory and hippocampal atrophy (fMRI task accuracy: r=&thinsp-0.32, p < 0.05; memory composite score: r=-0.34, p = 0.01) indicating that higher performance in the episodic memory task or memory composite score was associated with lower hippocampal atrophy (Fig. 3). There were no correlations between measures of spatial abilities tasks and hippocampal atrophy (fMRI task performance: r=&thinsp-0.07, p=0.62; spatial abilities composite score: r=-0.25, p=0.07).

Age was significantly correlated with hippocampal atrophy (r=0.46, p<0.001), episodic memory fMRI task performance (r=-0.49, p<0.001) and the composite scores (memory: r=-0.31, p<0.05; spatial abilities: r=-0.29, p<0.05). This indicated higher hippocampal atrophy and lower task performance with increasing age. There was no significant correlation between performance in the spatial abilities fMRI task and age (r=-0.21, p=0.14)

Cook's distance plots did not indicate any influential data points (Cook's distances larger than 0.5) in the correlations.

When controlled for age, no correlations were significant (episodic memory task performance and hippocampal atrophy: r =&thinsp-0.12, p = 0.39; memory composite score and hippocampal atrophy: r=-0.24, p = 0.09).

### Blood-based biomarkers

Seven participants were carriers of at least 701 one APOE  $\varepsilon$ 4 allele. Furthermore, we analyzed 702 A $\beta_{42/40}$  ratio (mean = 0.068, SD = 0.014), pTau181 703 (mean = 2.34 pg/ml, SD = 1.22), glial fibrillary 704 acidic protein (mean = 126.86 pg/ml, SD = 60.21), 705

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Table 3
Association between blood-based biomarkers, behavioral composite scores, sex, and hippocampal atrophy (n = 38). For the dichotomous
variable APOE $\varepsilon$ 4 carrier (yes/no) and sex (female/male) Welch's t-tests were performed and t-values are reported. For the other blood-based
biomarkers partial Pearson's correlations were calculated and partial correlation coefficients are reported

Blood-based biomarkers		Memory composite score	Spatial abilities composite score	Hippocampal atrophy
APOE4 carrier (Welch's t) 0.00		1.14	0.24	
Sex (Welch's t) $-1.2$		1.37	0.77	
Amyloid- $\beta_{42/40}$ ratio 0.20		0.20	0.06	-0.55**
(partial r)				
pTau181 (partial r) 0.07		0.07	-0.13	-0.13
*p<0.05, * 0.75 0.50	** <i>p</i> <0.001.		nory composite score	
Accuracy Accuracy 0.00	•		₽ -2- •••	
	-2 -1 0	1 2 3	-2 -1 0	1 2 3
Hippocampal atrophy			Hippocampal atrophy	

Fig. 3. Scatterplots illustrating correlations for episodic memory fMRI task performance and memory composite score with hippocampal atrophy. Grey bands indicate standard errors.

and neurofilament light chain (mean = 22.9 pg/ml, 706 SD=11.21). Based on currently recommended cut-707 off scores, ratios lower than 0.06 in the A $\beta_{42/40}$  ratio 708 indicate amyloid positivity [57]. In our sample, this 709 included eight participants. For pTau181, a cut-off of 710 1.8 pg/ml has been suggested for amyloid positivity 711 [57], which indicated 18 participants with amyloid 712 positivity. This pTau181 cut-off score is in-line with 713 previous research [58]. Three participants reached 714 the cut-off scores for amyloid positivity in both the 715 A $\beta_{42/40}$  ratio and pTau181. Therefore, we consid-716 ered 23 participants as positive for AD pathology 717 related blood-based biomarkers. There was a signif-718 icant association between hippocampal atrophy and 719 A $\beta_{42/40}$  ratio (r=-0.55, p<0.001) when controlling 720 for age. Please see Table 3 for the complete results 721 of the performed Welch's t-test and partial Pearson's 722 correlation analyses. 723

The correlation between A $\beta_{42/40}$  ratio and hippocampal atrophy remained significant also when the correlation analysis was additionally controlled for sex and years of education (*r*=-0.60, *p* < 0.001).

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### fMRI task performance

The accuracy levels across all conditions in the two 729 fMRI tasks were significantly above the chance level 730 of 50% (cued recall: t(51)=-4.59, p < 0.001; recog-731 nition: t(51)=-8.71, p < 0.001, translation: t(51)=-732 10.58, p < 0.001; rotation: t(51)=-10.40, p < 0.001; 733 luminance translation: t(51) = -11.49, p < 0.001; lumi-734 nance rotation: t(51)=-10.54, p < 0.001). Therefore, 735 we assume that both tasks were appropriately 736 designed regarding task duration and level of diffi-737 culty. 738

### 739 Model 1: Episodic memory fMRI task

A whole brain analysis (constrained to the grey 740 matter mask) for the cued recall>control contrast 741 in the face-occupation episodic memory fMRI task 742 showed significant activity in the parietal and occip-743 ital lobe. Therefore, we considered the episodic 744 memory task and the selected contrast as appropri-745 ate and conducted further analyses (please see the 746 Supplementary Material for details). Study site, total 747 intracranial volume, age, and sex were included as 748 covariates. 749

### Model 1.1: Compensation related to performance in the episodic memory fMRI task

A mask for task-related activity positively correlated with hippocampal atrophy ( $p_{uncorrected} < 0.01$ ) was calculated in a first step in the cued recall > control contrast (Fig. 4A).

In a second step, the same contrast was calculated, 756 but this time for activity that was positively correlated 757 with fMRI task performance (i.e., accuracy). Task 758 accuracy was not correlated with significant brain 759 activity in any brain region when corrected for mul-760 tiple testing (pFWE < 0.05). Without correction for 761 multiple testing, the strongest activity before masking 762 was located in the left lateral orbital gyrus (t = 3.49; 763 puncorrected = 0.001; peak x, y, z coordinates: -40, 764 40, -18) and the left cerebral white matter/occipital 765 fusiform gyrus (Fig. 4B). 766

Finally, the binary mask was used (inclusive masking) in the same contrast for activity that was positively correlated with episodic memory fMRI task performance. There were no significant clusters after masking (pFWE < 0.05 or p<sub>uncorrected</sub> < 0.001).

### Model 1.2: Compensation related to the memory composite score

An identical inclusive masking analysis with the memory composite score instead of episodic memory fMRI task accuracy did not show any significant results (pFWE < 0.05 or p<sub>uncorrected</sub> < 0.001). Please see the Supplementary Material for details.

### 779 Model 2: Spatial abilities fMRI task

Α whole brain analysis ([transla-780 tion+rotation]>luminance conditions contrast, 781 constrained to the grey matter mask) with study 782 site, total intracranial volume and age as covariates 783 was calculated and revealed several clusters with 784 significant activity in the parietal lobe (please see 785

the Supplementary Material for details). Therefore, we considered the selected spatial abilities contrast as appropriate for the planned analyses.

### Model 2.1: Compensation related to performance in the spatial abilities fMRI task

We calculated also for the spatial abilities fMRI paradigm task-related activity positively correlated with hippocampal atrophy ( $p_{uncorrected} < 0.01$ ). This showed the strongest activity in the left subcallosal area (t=4.78;  $p_{uncorrected}$ =0.000; peak x, y, z coordinates: -4, 10, -24), cerebellar vermal lobules I-V (t=4.18;  $p_{uncorrected}$ =0.000; peak x, y, z coordinates: 0, -54, -16), and the left cerebral white matter/superior frontal gyrus (t=3.91;  $p_{uncorrected}$ =0.000; peak x, y, z coordinates: -20, 12, 46) (Fig. 5A).

Task accuracy was not positively correlated with significant brain activity when corrected for multiple testing (pFWE < 0.05). Without correction for multiple testing (p<sub>uncorrected</sub> < 0.001) the only significant clusters were located in the right medial orbital gyrus (t = 4.62; p<sub>uncorrected</sub> = 0.000; peak x, y, z coordinates: 14, 26, -30; t = 3.91; p<sub>uncorrected</sub> = 0.000; peak x, y, z coordinates: 18, 18, -28; t = 3.78; p<sub>uncorrected</sub> = 0.000; peak x, y, z coordinates: 12, 20, -28) and the left supramarginal gyrus (t = 3.59; p<sub>uncorrected</sub> = 0.000; peak x, y, z coordinates: -66, -32, 32) (Fig. 5B).

After inclusive masking, one isolated effect with significant activity was located in the left supramarginal gyrus without correction for multiple testing  $(t=3.64; p_{uncorrected} = 0.000; peak x, y, z coordinates: -66, -32, 32)$  (Fig. 5C).

### Model 2.2: Compensation related to the spatial abilities composite score

A model with hippocampal atrophy as mask  $(p_{uncorrected} < 0.01)$  for activity positively correlated with the spatial abilities composite score also did not show any significant results (pFWE < 0.05 or  $p_{uncorrected} < 0.001$ ). Please see the Supplementary Material for details.

Repetition of fMRI analyses in a subsample with positive blood biomarkers for amyloid positivity

### Model 1.3: Compensation related to performance in the episodic memory fMRI task in a subsample with positive blood biomarkers for amyloid positivity

A contrast for the positive correlation between activity and hippocampal atrophy was calculated

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Fig. 4A. Greater activity related to greater hippocampal atrophy in the episodic memory task (cued recall>control contrast,  $p_{uncorrected} < 0.01$ ), used as mask. Activity was detected in the left temporal pole and the right middle cingulate and occipital fusiform gyrus. b) Greater activity related to high episodic memory task accuracy in the cued recall>control contrast was located in the left lateral orbital gyrus and the left cerebral white matter/occipital fusiform gyrus ( $p_{uncorrected} < 0.001$ , before masking). R, right; P, posterior.



Fig. 5A. Greater activity related to greater hippocampal atrophy in the spatial abilities task ([translation+rotation]>luminance conditions contrast,  $p_{uncorrected} < 0.01$ ), used as mask. Activity was detected in the left subcallosal area, the cerebellar vermal lobules I-V and the left cerebral white matter/superior frontal gyrus. b) Greater activity related to high spatial abilities task accuracy (before masking) was located in the right medial orbital gyrus and the left supramarginal gyrus ( $p_{uncorrected} < 0.001$ ). c) After inclusive masking a significant cluster in the left supramarginal gyrus was detected ( $p_{uncorrected} < 0.001$ ). R, right; P, posterior.

 $(p_{uncorrected} < 0.01)$  (Fig. 6A). The clusters with 834 strongest activity were detected in the left middle 835 temporal gyrus (t = 5.50; p<sub>uncorrected</sub> = 0.000; peak x, 836 y, z coordinates: -66, -10,-20), the right angular gyrus 837  $(t = 5.41; p_{uncorrected} = 0.000; peak x, y, z coordinates:$ 838 48, -64, 18) and left cerebral white mater/temporal 839 pole (t = 5.27; p<sub>uncorrected</sub> = 0.000; peak x, y, z coor-840 dinates: -44, 4, -22). 841

Task accuracy was not positively correlated to significant brain activity when corrected for multiple testing (pFWE < 0.05). Without correction for multiple testing, the strongest activity was located in the right calcarine cortex (t=4.80; p<sub>uncorrected</sub> = 0.000; peak x, y, z coordinates: 8, -84, -2), the left middle frontal gyrus (t=4.70; p<sub>uncorrected</sub> = 0.000; peak x, y, z coordinates: -26, 6, 56) and the left cerebral white

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Fig. 6A. Greater activity related to greater hippocampal atrophy in the episodic memory task (cued recall > control contrast,  $p_{uncorrected} < 0.01$ ), used as mask in a subsample with positive blood biomarkers for amyloid positivity. Activity was detected in the left middle temporal gyrus, the right angular gyrus and left cerebral white mater/temporal pole. b) Greater activity related to high episodic memory task accuracy (cued recall > control contrast, before masking) was located in the right calcarine cortex, the left middle frontal gyrus, the left cerebral white matter and opercular part of the inferior frontal gyrus. R, right; P, posterior.

matter/opercular part of the inferior frontal gyrus  $(t = 4.46; p_{uncorrected} = 0.000; peak x, y, z coordinates: -48, 16, 16)$  (Fig. 6B).

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Also in this contrast no voxel survived when the binary mask for hippocampal atrophy was applied  $(p_{uncorrected} < 0.001)$ .

# Model 1.4: Compensation related to the memory composite score in a subsample with positive blood biomarkers for amyloid positivity

A model with hippocampal atrophy as mask  $(p_{uncorrected} < 0.01)$  for activity positively correlated with episodic memory task accuracy did not show any significant results (pFWE < 0.05 or  $p_{uncorrected} < 0.001$ ). Please see the Supplementary Material for details.

#### 865 Model 2.3: Compensation related to

## performance in the spatial abilities fMRI task in a subsample with positive blood biomarkers for amyloid positivity

The [translation+rotation]>luminance con-869 ditions contrast showed the strongest activity 870  $(p_{uncorrected} < 0.01)$  positively correlated with 871 hippocampal atrophy in the left middle frontal gyrus 872  $(t = 5.24; p_{uncorrected} = 0.000; peak x, y, z coordinates:$ 873 -40, 2, 60), the left superior frontal gyrus (t = 4.95; 874 puncorrected = 0.000; peak x, y, z coordinates: -24, 875 10, 66), and the left superior frontal gyrus medial 876 segment (t = 4.81; p<sub>uncorrected</sub> = 0.000; peak x, y, z 877 coordinates: -6, 64, 24) (Fig. 7A). 878

No significant results remained after pFWE < 0.05</li>
 correction when positive correlations with the spatial
 abilities task accuracy were calculated. Without cor-

rection for multiple testing ( $p_{uncorrected} < 0.001$ ) the only significant cluster was located in the right medial orbital gyrus (t = 4.56;  $p_{uncorrected} = 0.000$ ; peak x, y, z coordinates: 14, 26, -30) and close by in the gyrus rectus (t = 3.68;  $p_{uncorrected} = 0.001$ ; peak x, y, z coordinates: 6, 24, -32) (Fig. 7B).

After inclusive masking no significant voxel survived (p<sub>uncorrected</sub> < 0.001).

### Model 2.4: Compensation related to the spatial abilities composite score in a subsample with positive blood biomarkers for amyloid positivity

A model with hippocampal atrophy as mask ( $p_{uncorrected} < 0.01$ ) for activity positively correlated with the spatial abilities composite score also did not show any significant results (pFWE < 0.05 or  $p_{uncorrected} < 0.001$ ). Please see the Supplementary Material for details.

### DISCUSSION

In the present study, we investigated if neuronal compensation existed in a sample of older adults with SCD. We employed two fMRI tasks targeting different cognitive domains. Both tasks should induce activity in the parietal lobe, which is affected by neuropathology early in the course of AD.

We did not find strong evidence for compensatory brain activity in either of the two tasks. The model for the complete sample in the spatial abilities task (model 2.1) showed a very small effect in the left supramarginal gyrus uncorrected for multiple comparisons. This brain region has been associated with working memory and attention. It is part of the fronto882

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Fig. 7A. Greater activity related to greater hippocampal atrophy in the spatial abilities task ([translation+rotation]>luminance conditions contrast,  $p_{uncorrected} < 0.01$ ), used as mask in a subsample with positive blood biomarkers for amyloid positivity. Activity was detected in the left middle frontal gyrus, the left superior frontal gyrus and the left superior frontal gyrus medial segment. b) Greater activity related to high spatial abilities task accuracy (before masking) was located in the right medial orbital gyrus and the gyrus rectus ( $p_{uncorrected} < 0.001$ ).

parietal attentional control network and crucial for
spatial working memory [59]. Another study reported
compensatory activity in the left parietal lobe in early
neurodegeneration [11], which is located closely to
the effect we detected.

However, in fMRI studies, a common minimal 918 cluster size is ten voxels [59]. Regarding the very 919 small size of three voxels, the small t-value (t=3.64)920 and the location of our finding at the outer grey mat-921 ter/CSF border, this result must be interpreted with 922 caution. In a subsample with blood biomarkers indi-923 cating amyloid positivity, and in subsamples based on 924 residuals of regressions of task performance and hip-925 pocampal atrophy, we found no evidence for neuronal 926 compensation. 927

Whole brain analysis for the contrast cued 928 recall>control in the face-occupation task showed 929 the strongest activity in the occipital lobe and the left 930 ventral diencephalon. The activity over the occipi-931 tal lobe was partially caused by the visually different 932 stimuli in both conditions [46]. The cluster includ-933 ing the left diencephalon encompassed also structures 934 like the parahippocampal gyrus and the hippocampus, 935 which can be expected when using a task targeting 936 episodic memory [16]. The whole brain analysis for 937 the [translation+rotation]>luminance conditions con-938 trast in the spatial abilities task showed the strongest 939 activation in the inferior occipital gyrus encompass-940 ing several structures from the parietal and occipital 941 lobe in both hemispheres. This corresponds to the 942 activity pattern reported for young adults in this task 943 [49]. Our results show that the selection of tasks and 944 contrasts was appropriate for eliciting activity in the 945 parietal cortex. 946

Previous research supports the existence of neuronal compensation [11, 13, 14, 26]. However, there

are substantial differences between these and the present study, which might explain the different findings. The other studies included different samples for healthy controls and participants affected by SCD [11, 13, 14] and MCI [26]. To fulfil the criteria of successful compensation, greater activity has to be related to better performance. In studies including SCD as well as healthy controls this correlation would appear in the SCD sample only [60]. This has been the case in the studies from Erk et al. [13] and Corriveau-Lecavalier et al. [11, 61]. As only these two studies fulfil the criteria for successful compensation in SCD our results indicate that compensation in this population is not a stable finding.

While the absence of clear compensatory brain activity in our full sample might be due to the inclusion of subjects without neuropathology this explanation is less likely in the subset with positive blood biomarkers for amyloid positivity. For the identification of amyloid positivity, we relied on relatively new blood biomarkers for amyloid-B and pTau181. The A $\beta_{42/40}$  ratio has shown to be a good measure for amyloid PET status [62]. In our sample, eight participants were positive for amyloid pathology according to the cut-off score. To increase sample size, we also included participants with high plasma pTau181 values. This blood biomarker predicted amyloid PET positivity [63]. It is possible that current plasma pTau181 measures are not sensitive enough to differentiate within a sample of SCD for amyloid positivity yet. This assumption is supported by the lack of a correlation between pTau181 values and our measure of hippocampal atrophy (r=-0.13, p=0.44), which was correlated with the A $\beta_{42/40}$  ratio (r=-0.55, p<0.001) also when corrected for age.

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It is possible that different patterns of brain activity 985 in neuronal compensation occur in our study sample. 986 Therefore, it might be interesting to investigate single 987 subject data to identify groups with different patterns 988 of compensatory activity in a future study. Another 989 statistical approach would be to investigate fMRI data aan with dimensional reduction methods following, e.g., 991 an independent component analysis [64]. It is pos-992 sible that such alternative approaches would lead to 993 different results but with the downside of inflating the 994 number of tests. 995

### 996 Limitations

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We included no sample of healthy subjects, which might have facilitated the detection of neuronal compensation.

We used hippocampal volume as a proxy for dis-1000 ease load and therefore refer to it as hippocampal 1001 atrophy. This term reflects our interpretation of vol-1002 ume, but we have no knowledge on longitudinal 1003 changes in hippocampal size of participants. There-1004 fore, it is possible that some participants with high 1005 hippocampal atrophy according to our study results 1006 were actually born with a relatively small hippocam-1007 pus and no atrophy occurred. Data for blood-based 1008 biomarkers was available for 38 participants, result-1009 ing in a final sample of 23 participants with biomarker 1010 values indicating amyloid positivity. This sample size 1011 might have been too small to find subtle effects of 1012 early AD related pathology in brain activity. Addi-1013 tionally, in our sample only eight participants were 1014 positive for amyloid pathology according to the cut-1015 off score for the A $\beta_{42/40}$  ratio. A larger number might 1016 have been necessary to detect neuronal compensa-1017 tion. This limitation can also be applied to the sample 1018 as a whole. 1019

As mentioned in the introduction, SCD is nonspecific and can appear as an early sign of cognitive decline but also as consequence of psychiatric disorders [2]. Therefore, our sample probably included SCD due to different causes, while compensatory activity in SCD is mostly expected to be a result of beginning neurodegeneration. This heterogeneity might have reduced our ability to detect strong compensatory brain activity on the group level.

While our approach focused on increased brain activity, also reduced activity and network connectivity have been observed in SCD [65]. The authors of this review suggest a model where neuronal connectivity is related to SCD stage (i.e., after increased connectivity due to noisy signal propagation and potential compensation in early SCD connectivity decreases). In our sample we considered SCD as one category and did not include the onset of SCD as potential moderating factor of compensatory effects. But we expect hippocampal atrophy as an indicator of disease load to increase in the course of SCD.

### Conclusion

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Our study did not provide conclusive evidence for compensatory brain activity in older adults with SCD in tasks targeting episodic memory or spatial abilities. It is possible that SCD is too early in the process of neurodegeneration to elicit compensatory activity or that this activity is too divergent among individuals given the broad definition of SCD in combination with the sample size used. Future studies could emphasize on detecting compensation in the individual as interventions such a transcranial electric current stimulation could be adapted to the individual's pattern of compensation.

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### **CONFLICT OF INTEREST**

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### DATA AVAILABILITY

The relevant data for this publication is openly available in the "Bern Open Repository and Information System" at https://doi.org/10.48620/66.

### 1073 SUPPLEMENTARY MATERIAL

The supplementary material is available in the
electronic version of this article: https://dx.doi.org/
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