Hippocampus' co-atrophy pattern in dementia deviates from covariance patterns across the lifespan

Running title: **Hippocampus' co-plasticity and co-atrophy**

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Abstract

The hippocampus is a plastic region and highly susceptible to aging and dementia. Previous studies explicitly imposed *apriori* models of hippocampus when investigating aging and dementia specific atrophy but led to inconsistent results. Consequently, the basic question of whether macro-structural changes follow a cytoarchitectonic or functional organization across the adult lifespan and in age-related neurodegenerative disease remained open. The aim of this cross-sectional study was to identify the spatial pattern of hippocampus differentiation based on structural covariance with a data-driven approach across structural magnetic resonance imaging data of large cohorts (n=2594). We examined the pattern of structural

covariance of hippocampus' voxels in young, middle-aged, elderly, mild cognitive impairment and dementia disease samples by applying a clustering algorithm revealing differentiation in SC within the hippocampus. In all the healthy and in the mild cognitive impaired participants, the hippocampus was robustly divided into anterior, lateral and medial subregions reminiscent of cytoarchitectonic division. In contrast, in dementia patients, the pattern of subdivision was closer to known functional differentiation into an anterior, body and tail subregions. These results not only contribute to a better understanding of co-plasticity and co-atrophy in the hippocampus across the lifespan and in dementia, but also provide robust data-driven spatial representations (i.e. maps) for structural studies.

Keywords: dementia, temporal lobe, structural covariance, parcellation, elderly

Abbreviations: 1000BRAINS = MRI dataset from Forschungszentrum Juelich, AD = Alzheimer's disease, ADNI= Alzheimer's Disease Neuroimaging Initiative dataset, aRI = adjusted Rand Index, CA1= Cornu Ammonis subfield 1, CA2= Cornu Ammonis subfield 2, CA3= Cornu Ammonis subfield 3, CA4= Cornu Ammonis subfield 4, CamCAN = Cambridge Centre for Ageing and Neuroscience dataset, CAT12= Computational anatomy toolbox, CDR= Clinical dementia rating, eNKI= Enhanced Nathan Kline Institute-Rockland Sample, FWE = family wise error, HCP= Human Connectome Project dataset, IQR=interquartile range, MCI= mild cognitive impairment, OASIS3= Open Access Series of Imaging Studies dataset, SC = structural covariance, SPM= statistical parametric mapping

Introduction

The hippocampus is a notable brain region from its lifelong plasticity potential (Moreno-Jiménez *et al.*, 2019), which can be observed with microstructural and molecular investigations but also at the macro-structural level using morphologic measurements of structural MRI. From macro-structural studies, the plasticity of the hippocampus seems to relate to experience and more particularly to cognitive training (Maguire *et al.*, 2006; Boyke *et al.*, 2008). Relatedly morphological measurements of the hippocampus across individuals suggest an important inter-individual variability (Van Petten, 2004; Fleming Beattie *et al.*, 2017; Llera *et al.*, 2019).

Since aging and Alzheimer's disease atrophy patterns resemble each other, in particular, showing important atrophy in temporal lobes, several authors suggested that dementia simply

represents a more severe or accelerated aging process (Fjell *et al.*, 2014). It has been frequently pointed out that clinically normal individuals demonstrate an accumulation of amyloid-beta and tau pathologies in the hippocampus and entorhinal cortex suggesting that neurobiological features associated with Alzheimer's disease can also be found in apparently healthy elderly populations (Sperling *et al.*, 2019; Ziontz *et al.*, 2019). Thus the neurobiological relationship between healthy aging and dementia and in particular the hypothesis of dementia as a form of increased aging process remains controversial and poorly understood.

Most researches have focused on hippocampal atrophy assessed at the macro-structural level and as representing the most straightforward non-invasive estimates of age-related structural changes. In other words, a large amount of investigations have aimed to identify specific pattern of atrophy across hippocampus' organization. Two different models of hippocampus' organization were referred to: the subfield model (based on cytoarchitecture features) and the tripartite model differentiating regions along the longitudinal axis such as the head-body and tail (based on functional and large-scale connectivity features). Since subfields and subregions are suggested to be characterized by different neurobiological features, they are likely to be differently affected by ageing and pathological processes. Despite several studies have investigated this question, no convergence towards individual subfields and subregions as being specifically affected by atrophy has emerged from these studies hindering our understanding of the underlying mechanisms.

In sum, our fundamental understanding of structural changes in the human hippocampus across the adult life span and in dementia remain fairly limited, but several issues should be pointed out to account for the current state of art. First, as described above, most studies were based on an a-priori model of hippocampus organization while it is unclear which model is the most appropriate. On the one hand, one could expect macro-structural changes to be constrained by the topology defined by cytoarchitecture, but on the other hand, as plasticity has been related to behavioral function, one could expect macro-structural changes to follow the functional organization of the human hippocampus along the longitudinal axis. Second, partly related to the first conundrum, the question of whether the pattern of structural changes in aging and dementia follow a similar topological pattern remains as a completely open question.

In this study, we have probed morphological changes across large datasets of structural MRI in healthy subjects and dementia patients applying a data-driven approach to reveal latent

patterns of differentiation in the hippocampus. Using the pattern of covariance with other brain regions across individuals to guide the clustering, importantly, allows the integration of interrelationships between the hippocampus and the whole brain hence revealing a more systemic pattern of change.

To implement the aforementioned objectives practically, we used a parcellation approach applied on hippocampus' structural co-variance in five different age and disease groups: young, middle-aged, elderly adults, mild cognitive impairment patients (MCI) and patients with dementia coming from independent datasets. We use the term "co-variance" to refer to healthy life-span changes in structural co-variation, which are assumed to be driven mainly by co-plasticity (e.g. regions developing together) and partly by co-atrophy, especially in older adults (e.g. regions degenerating together). In contrast, in dementia, we expect co-variation to be primarily driven by co-degeneration of brain regions. Accordingly, we use the term "co-atrophy" in the context of dementia patients (even though technically, the same "structural covariance" measure was applied across age and disease groups.

In this framework, a data-driven approach of structural covariance offers a bottom-up examination of the topological patterns of co-plasticity/co-variation in the first adult life periods and co-atrophy in elderly and dementia. Importantly, we examined the stability of the pattern across datasets by using split-half cross validation and robustness across groups with bootstrapping approaches. We explored the possible mechanisms explaining these patterns by examining the similarity of these topological patterns with the pattern of functional organization of the hippocampus, and investigated the structural networks that underlie the different hippocampus subregions. Finally, we characterized these structural networks with regards to behavioral functions and compared these structural networks with functional networks.

Materials and methods

Datasets, cohort samples and age-phenotypical groups

We included six different datasets: Human Connectome Project (HCP) (http://www.humanconnectome.org), Enhanced Nathan Kline Institute-Rockland Sample (eNKI) (http://fcon_1000.projects.nitrc.org/indi/enhanced/), Cambridge Centre for Ageing and Neuroscience (CamCAN) (https://www.cam-can.org/) (Shafto *et al.*, 2014; Taylor *et al.*,

2017), 1000BRAINS from Forschungszentrum Juelich (https://www.frontiersin.org/articles/10.3389/fnagi.2014.00149/full), Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://adni.loni.usc.edu/) and Open Access Series of Imaging Studies (OASIS3) (https://www.oasis-brains.org/). From these datasets, we formed five cohort samples: young, middle-aged, elderly, MCI and dementia participants. The age range of the group of young adults was set to 20-35 years. In turn, the age range of the middle-aged group was 35-55 years and for the elderly, we set a conservative age range of 60-80 years. MCI and AD patients were selected within the same age range as the elderly group. For the dementia group we included patients with probable Alzheimer's type pathology by selecting Alzheimer's disease patients from the OASIS3 dataset and ADNI dataset, as well as the late cognitive impaired individuals from the ADNI dataset who are considered as patients at the early stage of Alzheimer's disease (Qiu *et al.*, 2014). The MCI group was formed by the participants with the diagnosis 'early MCI' (ADNI dataset) and by participants with a CDR score of 0.5 from the OASIS3 dataset. The demographic data of each study samples and groups are reported in Table 1 and Tab 2 below. The analyses of these data were approved by the ethical committee of the Heinrich Heine University Düsseldorf.

Structural MRI acquisition, preprocessing and structural covariance computation

Only 3T MRI anatomical scans were included in this study acquired with different scanning parameters (Tab. 3). All images were preprocessed with SPM12 and the CAT12 toolbox, running on Matlab R2016a. The normalization was performed with the DARTEL algorithm to the ICBM-152 template using both affine and non-linear spatial normalization. The MRI images were bias-field corrected and segmented into gray, white matter, and cerebrospinal fluid tissues. The gray matter segments were then modulated for non-linear transformations only and subsequently smoothed with an isotropic Gaussian kernel (full-width-half-maximum = 8).

We used a mask of the human hippocampus created in a previous study (Plachti *et al.*, 2019) from macro-anatomical atlas and cytoarchitecture maps. Structural covariance was computed by correlating hippocampal voxels with all other grey matter voxels using Pearson correlation, which were z-transformed. For each dataset, hundreds of bootstrap samples (corresponding to the size of the dataset) were created and a respective structural covariance

matrix was computed for each bootstrap sample (see Supplemental material Methods).

Parcellation – clustering of hippocampus' voxels— based on structural covariance

Clustering

To identify patterns of similar and different structural covariance among hippocampus voxels, we used an unsupervised clustering approach extensively applied in the field of brain parcellation. More precisely, for each voxel within the hippocampus, an individual structural covariance profile to all other brain voxels across subjects was computed. In the next step, hippocampus' voxels were clustered based on the similarity/dissimilarity of their profiles. As a clustering algorithm we applied the k-means ++ algorithm in Matlab identifying two to seven parcels. We used 255 iteration and 500 repetition parameters in line with Plachti *et al.* (2019) to allow comparison with previous parcellations.

Split-half cross validation as stability measure

In order to identify which cluster solution best summarized similarity and dissimilarity in the pattern of structural covariance of hippocampus' voxels, we used split-half cross validation to estimate the stability of differentiations. We divided each sample into halves 10 000 times (splits) and compared with the adjusted Rand Index (aRI) the convergence between the two halves. The aRI estimates the consistency of two clusterings and is adjusted for chance. It can have values between 0 (not similar at all) and 1 (identical). A higher convergence reflects a higher consistency of the clusterings indicating high stability. In order to quantify statistically the stability of the different cluster solutions, we performed an ANOVA.

Cross-dataset group parcellation

To obtain robust patterns of structural covariance parcellation in each age/disease group, we merged after the clustering the parcellation results from different datasets corresponding to the same age and disease group. This procedure aimed to extract patterns that captured the relevant features under investigation (e.g. aging or dementia effects) rather than dataset

specific effects (Jockwitz *et al.*, 2019). First, the clustering approach was applied on hippocampus' voxels structural covariance profiles within each sample and age group resulting in sample-group-specific matrices. We then concatenated the solution matrix of one sample (e.g. Young_HCP) with all the other samples (e.g. Young_eNKI, Young_CamCAN) belonging to the same age or disease group (e.g. Young) and applied bootstrapping (10 000 resampling) on the 'merged' solution matrix across bootstrap samples (see Supplemental material Methods and Fig. 1).

Clusters' covariance network and their relationship to functional large-scale networks

In order to identify the pattern of structural covariance underlying the clustering in each age/disease group (n=2584), we examined the network of structural covariance more specifically associated to each cluster. To do so, we used the general linear model as implemented in SPM, hence at the voxel level. Accordingly, at each voxel, the linear relationship with the average grey matter value of the cluster of interest is tested. This procedure provided some insight into the individual pattern of structural covariance of the different subregions of the hippocampus that have driven the clustering. As the clustering is not performed on any thresholded values but based on the full pattern of structural covariance, we here examined the map of structural covariance of each cluster across the whole brain at an uncorrected level of $P < 0.001$ with a threshold of T=1. Nevertheless, we additionally corrected for multiple comparisons using family wise error (FWE) rate at the significance level of $P < 0.05$ to examine the brain patterns that survived at a strict statistical threshold (Supplementary Fig. 7).

To test whether structural covariance networks in dementia follow functional co-activation networks, we examined the functional connectivity of the subregions derived in dementia but in a sample of healthy participants. Our underlying hypothesis was that the pattern of co-atrophy in dementia could mirror functional connectivity patterns observed in late life (but before dementia). To explore this question, we performed a similar general linear model analysis using resting-state fMRI time-series in the group of healthy elderly (n=428 in 1000BRAINS; EPI, 36 slices, TR=2.2 s, TE=30 ms, FOV = 200 x 200 mm^2, flip angel = 90 $^\circ$, voxel resolution =3.1 x 3.1 x 3.1 mm^3) for the hippocampus' subregions derived from the dementia group. Preprocessing included movement correction by affine 2-pass registration and alignment of the images to the first volume and to the mean of the volumes. The six

motion parameters and their first derivatives from the realignment step were regressed out. Spatial normalization was performed to the MNI-152 Template for the average EPI scans for each subject using the unified segmentation approach. Images were band-pass filtered with cut-off values of 0.01-0.08 Hz and smoothed with the isotropic Gaussian kernel (full-width-half-maximum = 5 mm). Denoising was performed using white-matter and CSF signal regression.

For each grey matter voxel, a linear relationship with the average BOLD-response of the cluster of interest was computed. In this way, we obtained the functional connectivity network of each individual cluster and contrasted it against the whole brain pattern of association of other clusters.

Clusters' covariance network and their behavioral associations

After having identified the structural covariance network for each cluster, we characterized those networks in terms of associated behavioral functions using NeuroSynth database (https://neurosynth.org/) and its cognitive decoding tool with above 1 300 terms included. For the most frequent terms reported in the literature (such as "episodic memory"), NeuroSynth provides meta-analytic maps of the most frequently associated voxels in activation studies. It therefore offers the possibility to compare any given brain pattern, such as the whole brain structural co-variation patterns in the present study, to the collection of maps related to each term using the cognitive decoding tool. Accordingly, we used the uncorrected whole-brain maps of each cluster and ran Pearson correlations between our structural covariance maps and the meta-analytic maps of NeuroSynth. As our objective here was not to identify specific behavioral functions associated to a specific network but rather to identify the broad pattern of behavioral associations of cluster's network, we included all correlations for associated terms above 0.1, we excluded non-behavioral terms (e.g. hippocampus, dementia) and summarized similar lexical terms into a summary label (e.i. 'emotions', 'affect', 'happy', 'fear' -> emotion). The pattern of associated behavioral terms, which could differ in number depending on the spatial extent the of clusters' covariance pattern, was then interpreted qualitatively rather than with regards to magnitude of association.

Data availability statement

The data that support the findings of this study are available from open science initiatives reported and cited above. Code can be shared upon reasonable request from the corresponding author. The derived clusters are available at (http://anima.fz-juelich.de/) as ROI in .nii format.

Results

Stable clustering level

We used split-half cross-validation (10 000 splits) to identify the most stable cluster solution based on similarity across splits as measured by the aRI index. We performed a 6 (datasets: HCP, eNKI, CamCAN, 1000BRAINS, ADNI, OASIS3) x 6 (cluster solution: 2-7) ANOVA with the aRI as dependent variable. The ANOVAs were performed separately for each hemisphere.

Overall, examining cluster solutions' main effect $F(5,839964) = 32365.18$, $P < 0.001$), in the right hippocampus, parcellations into 2 and 3 clusters were the most stable solutions even though the differences between all cluster solutions were marginal: 2 (M=0.97,), 3 (M=0.96), 4 (M=0.95) (Fig. 1A). For the left hippocampus, cluster solution two and three were also the most stable: 2 (M= 0.97), 3 (M= 0.96), 4 (M= 0.94), $F(5,839964) = 25194.75$, $P < 0.001$(Fig. 1A). The significant interaction effects in right and left hippocampi indicated that the stability of parcellations was dependent on dataset, $F(25, 839964) = 2006.7$, $P < 0.001$, $F(25,839964) = 4884.36$, $P < 0.001$ (Supplementary Fig. 2).

In line with previous clustering studies, our first exploration showed a relatively linear decrease in the stability as the number of cluster increases, suggesting that the simpler, more parsimonious models are the most robust ones (additionally supported by silhouette plots in Supplemental material 2.2). In particular here, the 2- and 3- cluster solutions are the most stable levels of differentiation.

Similarity/consistency of the hippocampal differentiation

To further ensure that the stability of cluster solutions 2-4 was driven by intrinsic properties of the structural covariance pattern rather than by intrinsic properties of the dataset, we examined the pattern of similarity (measured by the aRI) between the different cohort samples (Fig. 1B).

The inspection of the similarity matrices revealed that, cluster solution 2 showed a general pattern of high similarity, whatever the dataset or age group. This suggested a global differentiation being robust across data and age/disease group (Fig. 1B). The 3-cluster solution mainly and remarkably showed a high within group (age and disease) and between group consistency suggesting a differentiation pattern driven by intrinsic features of the age/disease groups rather than by the intrinsic features of the dataset. This suggests that neurobiological rather than technical factors specific to the dataset guided the parcellation.
In contrast, the 4-cluster solution showed high within age group consistency only for the healthy elderly group in the right hippocampus, questioning its usability to study lifespan and disease related changes. Finally, the higher clustering levels (5, 6 and 7-cluster solution) showed overall relatively low similarity between samples (Supplementary Fig 2). Thus, the investigations of consistency/similarity between samples supported the focus on the 3-cluster solution as the most stable and most likely biological relevant pattern of differentiation of hippocampus' voxels.

In sum, our first 'bottom-up' examination of the differentiation of the hippocampus based on structural covariance across different datasets suggested that a 3-cluster solution could represent the data in a stable manner. Furthermore, our examination of consistency within age and disease group suggested that this high stability is not primarily driven by characteristics that were intrinsic to the dataset but rather by characteristics that were intrinsic to the population group and hence driven by neurobiological factors. Thus, altogether, hippocampus voxels within different age/disease groups could be optimally summarized with a 3-cluster solution ideally applicable to study lifespan and disease alterations. Importantly, such parsimonious 3-partition model also meets previous theories on hippocampus' organization.
Even though cluster solution 2 and 4 displayed high stability and consistency compared to higher differentiations, they were either less informative as in the case of cluster solution two (Supplementary Fig. 5) or demonstrated qualitatively divergent parcellations less comparable across age/disease group as in the case of cluster solution four (Supplementary Fig. 5). Building on these explorations of the data and previous knowledge, we then focused on the 3-cluster solution pattern.

Cross-dataset age and disease group parcellation

After deriving parcellations in each cohort sample, we merged them to obtain a robust pattern of differentiation of hippocampus voxels for five different age and disease groups: young, middle-aged, elderly, MCI and dementia patients using a bootstrapping approach to further promote stability. This aggregation was done separately for the left and right hippocampi. Nevertheless, a very symmetrical pattern of differentiation could be observed across hemispheres. For both hippocampi, our maps (Fig. 2) showed a very similar pattern for the young, middle-aged, elderly and the MCI group. This pattern highlighted a division in the medial-lateral dimension of the hippocampus' body and to some extent, of the tail while the head appeared as a relatively homogeneous region. This pattern replicated the findings from our previous parcellation work in the hippocampus performed in a sample of young participants from the HCP dataset (Plachti *et al.*, 2019), and as already highlighted in our previous study, is reminiscent of the medial-lateral differentiation between CA and subiculum subfields known from cytoarchitecture. Of note, it seemed that with increasing age the head cluster decreased slightly in size, while the medial (blue) cluster expanded into the tail area and the lateral (green) cluster expanded into the anterior direction (Fig. 2).

Remarkably, the differentiation of the hippocampus in the dementia group deviated from the pattern that was observed in healthy population across adult age. Despite the anterior subregion also appeared as a relatively homogeneous region, the lateral (green) cluster was focused on the hippocampus body while the medial (blue) cluster appeared more prominent in the tail. As illustrated in Figure 2, this pattern was reminiscent of the functional differentiation along the anterior-posterior dimension (and hence "head-body-tail" tripartite model) observed in parcellations using large-scale functional connectivity. In order to further quantitatively evaluate these apparent divergences and resemblances, we compared the similarity of the age and disease groups among each other and with the functional map of the hippocampus derived in healthy adult fMRI data (Plachti *et al.*, 2019) using the aRI.

Strikingly, the highest similarity with the hippocampus' functional map was found for the parcellation pattern obtained in dementia. This finding suggested that over time, the structural changes in the hippocampus in the pathological condition of dementia followed the large-scale functional organization of the hippocampus. Interestingly, this tendency was higher for the right than for the left hippocampus. Finally, it is worth noting that the pattern in participants with MCI was more similar to the healthy middle-aged and elderly participants than to the pattern observed in dementia.

Whole brain structural covariance patterns of each cluster

In order to better understand the structural covariance patterns that drove the differentiation among hippocampus' voxels in each age/disease group, we examined the specific structural covariance pattern of each cluster and this, separately in each age/disease group. The structural covariance networks for young, elderly adults and dementia patients are presented below while the results obtained in middle aged and MCI participants (that were in line with other non-demented groups) are presented in Supplementary Fig. 6.

In young participants the (red) anterior cluster was associated with wide fronto-temporal and parietal networks including frontal medial cortex, superior frontal gyrus, orbitofrontal cortex, cingulate cortex, temporal lobe, parahippocampal gyrus, (pre-)cuneal cortex, calcarine cortex, lingual gyrus and occipital pole. In addition, the putamen, pallidum, amygdala, insular cortex belonged to this network. A similar pattern was found in healthy elderly participants despite a slight expansion, additionally covering the inferior frontal gyrus, the whole cerebellum, pre- and postcentral gyri (Fig. 3).

The lateral (green) cluster in the young group was mainly associated with subcortical structures such as putamen, pallidum, nucleus caudatus, thalamus but also with the cingulate gyrus, lingual gyrus, precuneous cortex and intracalcarine/supracalcarine cortex. Additionally, frontal and temporal brain regions were included such as frontal orbital cortex, frontal operculum cortex, inferior frontal gyrus, pars opercularis and superior temporal gyrus. In the older group, this network mainly reduced to the parieto-occipital (posterior cingulate cortex, precuneous, lingual and intracalcarine gyrus) and frontal medial (frontal medial cortex, subcallocal cortex, frontal pole) brain regions reminiscent of the Default mode network.

The blue medial cluster in the group of young adults was mostly related to middle frontal, middle temporal gyri, cerebellum and lateral occipital cortex. Subcortical regions such as the caudate and thalamus, but also the insula were included. Interestingly, the (blue) medial cluster showed in the group of healthy elderly a very broad pattern of structural covariation (Fig 3), especially in the posterior brain regions (e.g. parietal, occipital lobes and motor related regions: cerebellum, pre-postcentral gyrus, thalamus, putamen, but also occipital gyrus, superior parietal lobule, and temporal gyri). Some smaller associated regions were also found in the inferior frontal and middle frontal cortex.

In contrast, in the group of patients with dementia, the pattern of structural covariance of each cluster was less spatially extended compared to all the other groups (Fig 3). Furthermore, the

pattern was also qualitatively different when compared to the patterns of the three clusters in the other age/disease groups confirming that the differentiation into subregions within the hippocampus itself is qualitatively different and did not follow the known pattern of healthy aging. Hence, the (green) lateral-body cluster was not associated with posterior subcortical structures as the lateral (green) cluster in other groups but rather was more specifically associated with structures in the frontal (inferior frontal gyrus pars opercularis, frontal pole, opercular gyrus), temporal (middle temporal gyrus, Heschl's gyrus) and occipital brain regions (Fig. 3). In contrast, the (blue) tail cluster was more associated with posterior brain regions (posterior parts of the temporal lobe, postcentral gyrus and (pre)cuneous, angular gyrus) while the anterior cluster was more associated with temporal, temporo-occipital fusiform cortex, and parietal regions loosing mainly its co-variation with frontal regions compared to younger healthy adults.

Because of apparent similarity between structural differentiation of the hippocampus in the dementia group with the functional organization model of the hippocampus known from previous studies in the healthy population, we further explored the relationship between functional and structural networks. More concretely, we investigated the pattern of resting-state functional connectivity in the later life period of healthy participants (i.e. in healthy older adults) of the hippocampus' cluster derived in dementia patients. This exploratory analysis suggested that the functional networks of the anterior and the lateral clusters that can be observed in an aging population are very similar to their structural networks observed in patients with dementia hence further supporting the hypothesis of a an influence of large-scale functional interaction in the co-atrophy pattern in dementia.

Behavioral characterization of clusters' structural covariance networks

In order to explore whether the structural covariance patterns of each cluster could reflect functional networks subserving specific behavioral functions, we characterized the spatial pattern of each cluster's covariance network with regards to behavioral terms with NeuroSynth. Results of middle aged and MCI patients are presented in Supplementary (Fig. 10) while we here focused on the associations in the young, elderly and the dementia group, as showing a slightly different pattern.

Overall, the spatial pattern of the anterior (red) cluster was primarily associated with emotional, perceptual (olfactory, viewing) and self-related (autobiographical) terms, but also with other less ontologically defined terms such as faces, ratings and reactivity (Fig. 4).

Overall, this behavioral pattern pointed to an automatic and more perceptual-emotional processing and integration of information into self-related internal states. This behavioral profile of the anterior subregion was even preserved in dementia pathology. In contrast, the pattern of the lateral (green) and the medial (blue) clusters' diverged depending on the age and disease group. Whereas the medial blue clusters' networks in the group of healthy young adults was associated with visual processing of objects and places, in the group of elderly and dementia patients, however, it was behaviorally additionally associated with motor/movement and orientation (Fig.4).

Most changes in structural co-variation and behavior were observed for the lateral (green) cluster. In the group of young healthy adults the network was associated with motor-related behavior (e.g. motor, navigation), whereas in the elderly the behavioral association suggested an involvement of storing self-related information (e.g. autobiographic memory, episodic memory). In the group of dementia patients, on the other hand, the network was primarily associated with communication and social cognition, both of its own internal states (e.g. pain) as well as external information (e.g. comprehension, theory of mind). Overall, these results suggested that, the changes in the patterns of structural co-variation of the medial and lateral clusters over the life span and in pathology could be related to associations with different behavioral functions.

Discussion

The hippocampus is susceptible to senescence and neurodegenerative processes but the patterns of structural changes at the macro-scale revealed inconsistencies across studies. Observed changes in grey matter volume could be either constrained by micro-anatomical organization of the cytoarchitecture or follow an organization determined by lifelong functional large-scale networks.

In a previous recent study, we used a parcellation approach to study human hippocampus organization with a multimodal parcellation approach. We hence examined the pattern of structural covariance in the human hippocampus in healthy young adults and found a topology that mimics both medial-lateral differentiation from cytoarchitecture and anterior-posterior differentiation shown by functional connectivity profiles (Plachti *et al.*, 2019). A similar pattern was found in a very recent study using a similar population but different

parcellation approaches (Ge *et al.*, 2019), and was reproduced again in this study, hence suggesting that this pattern reflects a robust pattern of co-plasticity in young adults.

We here investigated if structural changes represented in co-variations in older age and dementia follow or deviate from the patterns of co-plasticity observed in young adults. Our results indicated that during aging the overall pattern of structural covariance follows the pattern of structural covariance observed in young adult age with some small differences discussed below. However, in participants with probable dementia disease, the pattern of co-atrophy in the hippocampus deviates from what was observed in these healthy populations. In patients with dementia, the co-atrophy seems to follow the functional large-scale networks with a pattern that resembles more than the functional model of hippocampus' organization than what was observed in other groups. Overall, the most prominent differences between groups in the differentiation patterns of the hippocampus were found in the body and tail whereas the head always appears as a uniform region. Group differences were shown not only in the topological pattern within the hippocampus, but also in the whole brain structural covariance pattern that drove the clustering and their associated behavioral associations.

Consistent pattern of head differentiation in hippocampus' structural covariance across the lifespan

Independent of age and disease, the head of the hippocampus, emerged consistently as one homogeneous subregion, except for some minor reductions with higher age and ongoing pathology. But the actual underlying covariance pattern of the anterior hippocampal subregion changed across age/disease groups. In young adulthood the anterior hippocampal co-variation pattern was characterized by a broad network extending across frontal, temporal and occipital lobes as well as (inferior) parietal regions. In accordance with the large spatial distribution of this network, behavioral associations showed a relatively broader spectrum including emotional, cognitive and perceptual processes. These results could suggest that the hippocampus head is a plastic region (based for example on cell proliferation in the dentate gyrus, (van Praag *et al.*, 2005) during the life span), which structure is modulated by rich functional interaction with large-scale brain networks subserving various behavioral functions. The structural covariance networks of the hippocampus head in early and late adulthood demonstrated that the anterior hippocampus co-varied with the same brain regions in both halves of healthy lifespan suggesting a perseverance of co-plasticity and resilience.

However, in dementia the structural covariance network of the anterior subregion decreased mainly to the temporal lobe suggesting a loss of network.

Consistent pattern of medial-lateral differentiation in hippocampus' structural covariance

Across different age groups of the healthy population, we found a consistent differentiation pattern along the medial-lateral dimension of the hippocampus dividing it into a lateral and a medial subregion. This pattern replicated previous findings and seemed to follow the cytoarchitectonic differentiation between the CA and subiculum subfields (Plachti *et al.*, 2019). Importantly, this pattern, like the head subregion, appeared to remain stable across the whole adult life span suggesting a very strong and robust scheme of structural covariance that should be referred to when studying structural changes with MRI in adults. This scheme was even further retained when subdividing the hippocampus into 4 subregions in healthy adults and MCI patients (Supplementary Fig. 5), even if, one additional cluster appeared either in the anterior or posterior-lateral region depending on the age/disease group. Even though the differentiation into a lateral and medial parcel was preserved over the lifespan, the lateral cluster decreased posteriorly with age and the medial cluster expanded into the tail. This change in the cluster pattern was reflected both in the associated structural pattern and the related behavioral associations.

The medial hippocampal subdivision showed a co-variation pattern with occipito-parietal, temporal (middle temporal gyrus), and frontal (inferior and middle frontal gyri) brain regions. Furthermore, the network included subcortical brain regions such as thalamus, caudate, and insula. With increasing age, the covariance network expanded highly in size, especially covering posterior brain regions. The shift from mostly anteriorly associated brain regions in younger years to posteriorly associated regions in elderly is not unusual for the hippocampus. It has already been reported in functional connectivity (Blum *et al.*, 2014; Stark *et al.*, 2019), in structural covariance studies (Li *et al.*, 2018), and for anatomical connectivity with strengthened connections to medial occipital regions (Maller *et al.*, 2019), which was in line with our results, even though the responsible mechanisms remain to be elucidated.

These alterations were also mirrored in the behavioral association patterns. While in younger adults visual cognition (e.g. object, place, encoding, familiarity) was prominent, in elderly, however, the behavioral spectrum expanded to language processing as well as to motor

related (learning) behavior. Both, structural co-variation networks and behavioral profiling, suggest that brain regions connected by the inferior longitudinal fasciculus (ILF) co-vary more likely with the medial subregion of the hippocampus. The ILF is an occipito-temporal association tract with close relationships to the occipital radiations and hippocampus through the tapetum (Herbet *et al.*, 2018). The ILF is behaviorally associated with visual object and face recognition, reading as well as lexical and semantic processing (Herbet *et al.*, 2018), which is in accordance with our behavioral profiling of the medial subregion across the lifespan.

While the medial cluster expanded into the tail during healthy aging, the lateral cluster decreased from the tail. The lateral subregion's co-variance network in young adulthood yielded primarily associations with subcortical regions (e.g. thalamus, caudate nuclei) and additionally with the parieto-occipital fissure. Anatomically those associated brain regions were reminiscent to some extent to the grey matter regions around the dorsal hippocampal commissure, being connected with posterior cingulum, tapetum, and fornix (Postans *et al.*, 2019). The dorsal hippocampal commissure is associated with learning, memory and recently also with recognition (Postans *et al.*, 2019). The fornix is the white matter output of the hippocampus through the tail (Amaral *et al.*, 2018) whereas the tapetum transfers information between hemispheres. The hippocampus is connected via the fornix with limbic structures (e.i. hypothalamus, thalamus, nucleus accumbens) (Douet and Chang, 2015), and has been suggested to play a major role in transferring information from short-term to long-term memory via the Papez circuit and is accordingly, involved in long-term memory encoding and retrieval (Eichenbaum *et al.*, 2007; Douet and Chang, 2015; Foster *et al.*, 2019).

Structural covariance pattern in the hippocampus in dementia resemble functional organization

In healthy population, structural covariance across the brain is assumed to reflect maturational, developmental and experience-based co-plasticity (Alexander-Bloch *et al.*, 2013; Geng *et al.*, 2017). In patients with neurodegenerative disorders, structural covariance across the brain could be expected to mainly reflect brain structure co-atrophy. The moderate to high convergence between structural covariance and task-(un)related functional connectivity (Reid *et al.*, 2016; Kotkowski *et al.*, 2018; Paquola *et al.*, 2018; Shah *et al.*,

2018) suggests that abnormalities in structural and functional network topology is predictive of brain disorders (Seeley *et al.*, 2009; Goodkind *et al.*, 2015) and weaker cognitive performance (Spreng and Turner, 2013; McTeague *et al.*, 2016; Montembeault *et al.*, 2016). However, the question remains fully open whether structural atrophy changes functional BOLD response (He *et al.*, 2007) or the other way around (Chang *et al.*, 2018). From a neuropathological standpoint, Alzheimer's pathology is assumed to follow a specific topological pattern distributed along large-scale networks (Braak and Braak, 1991; Corder *et al.*, 2000; Montembeault *et al.*, 2016). For example, amyloid-plaque distribution in the brain seems to follow functional organization mirrored in the Default mode network (DMN) (Klunk *et al.*, 2004; Buckner *et al.*, 2005; Montembeault *et al.*, 2016). Similarly, the spreading of tau neurofibrillary tangles seems to follow a functional pattern, which is not explained by spatial proximity (Franzmeier *et al.*, 2019). In other words, brain regions that are more likely to be functionally coupled together share a stronger tau covariance, which is not explained by pure spatial neighborhood. This apparent convergence between spatial distribution of pathology markers and the spatial organization of functional networks may be explained by the fact that synchronous neuronal firing establishes a network-based synaptogenesis (Katz and Shatz, 1996; Bi and Poo, 1999), which can then be assumed to be vulnerable to pathological processes.

Linking these neuropathological considerations to the pattern of differentiation based on structural covariance found in the hippocampus of patients with probable AD in this study, we can hypothesize that the pattern of co-atrophy in these patients followed the pattern of functional organization subserving broad behavioral functions. In this regard, we can note that the pattern of structural covariance networks of the hippocampal body in dementia patients in this study was associated with temporal and frontal regions in turn associated with comprehension, language, orthography and theory of mind. We hypothesize that the structural covariance network of the hippocampus' body reflects a functional network of higher cognitive functions of social cognition additionally supported by the functional co-activation pattern of the lateral-body subregion when applied to healthy elderly. It therefore emphasizes, that the hippocampal differentiation based on structural covariance in dementia follows functional differentiation. Overall our findings point to the necessity of accounting for hippocampus' functional organization related to large-scale networks subserving broad behavioral functions when studying hippocampus' structural changes at the macro-scale in dementia.

Table 1. Demographic data of all collected samples

Samples	Sample size (n)	Mean age (SD; age range)	% females	Education	CDR	MMSE
Young_HCP	n= 304	27.8 (SD=3.55; 22-34)	50.6%	SSAGA_Educ: 14.8 (SD= 1.75; 11-17); NAs: 0	/	29.0 (SD =1.07; 23-30); NAs: 0
Young_eNKI	n= 140	24.8 (SD=3.85; 20-34)	50%	SES-Adult Education code, 5.4 SD=0.8; 4-7; 14.8 (SD = 1.6; 11-18); NAs: 0	/	/
MiddleAged_eNKI	n= 72	43.6 (SD=5.7; 35-54)	52.7%	SES-Adult Education code, 5.5 (SD=1; 3-7); 15.1 (SD=2.3; 10-21); missing n=2	/	/
Old_eNKI	n= 76	68.3 (SD=5.5; 60-79)	51.3%	SES-Adult Education code, 6.0 (SD=1.0 4-7); 16.1 (SD=2.4; 12-24); NAs: 0	/	/
Young_ CamCAN	n= 94	28.4 (SD=3.97; 20-34)	50%	Education scoring: 6.2 (SD=1.7; 2-8); missing	/	29.4 (SD=1.17, 25-30); NAs: 0

				n=21		
MiddleAged_CamCAN	n =207	44.3 (SD=5.78; 35-54)	50.7%	5.7 (SD=1.8, 1-8); missing n=35	/	29.1 (SD=1.17, 26-30); NAs: 0
Old_CamCAN	n = 213	69.8 (SD=5.96; 60-79)	50.2%	5.0 (SD=2.2, 1-8); missing n=65	/	28.4 (SD=1.47, 25-30); missing n=1
Old_1000BRAINS	n = 492	66.9 (SD=4.24; 60-75)	50%	Education years: 13.7 (SD= 3.7, 3-27); missing n=1	/	/ Demtec: 15.2 (SD=2.3, 8-18); missing n=9
Old_ADNI	n = 139	71.6 (SD=4.65; 61-79)	51.7%	Education years: 16.6 (SD=2.6, 12-20); NAs: 0	CDR sum of boxes: 0.02, SD= 0.11, 0-0.5; NAs: 0	28.9 (SD=1.24, 24-30); NAs: 0
MCI_ADNI	n = 213	69.2 (SD=5.05; 60-79)	50.2%	Education years: 15.9 (SD=2.6, 10-20); NAs: 0	CDR sum of boxes: 1.22, SD=0.76, 0.5-4; NAs: 0	28.4 (SD=1.5, 23-30); NAs: 0
AD_ADNI	n = 219	71.0 (SD=5.42	51.1%	Education years: 16.1	CDR sum of	25.8 (SD= 3.0,

		; 60-79)		(SD= 2.6, 11-20); NAs: 0	boxes: 2.9, SD= 1.8, 0.5-10; NAs: 0	19-30); NAs: 0
Old_OASIS3	n = 298	70.3 (SD=4.42; 60-79)	50%	Education years: 16.0 (SD=2.7, 8-24); NAs: 0	0, SD = 0, 0-0; NAs: 0	28.8 (SD=1.8, 9-30); missing n =2
MCI_OASIS3	n = 74	70.9 (SD=4.58; 61-79)	50%	Education years: 15.3 (SD=2.7, 8-20); NAs: 0	0.5, SD=0, 0.5-0.5; NAs: 0	26.7 (SD=3.4, 13-30); missing n=2
AD_OASIS3	n = 53	69.9 (SD=5.58; 60-79)	47.2%	Education years: 15.1 (SD=2.8, 11-20); NAs: 0	0.92, SD=0.57, 0-2; NAs: 0	23.5 (SD=4.8, 10-30); missing n=1

Table 2. Demographic data of the age and disease groups created from independent samples

Phenotypical group	Size (n)	Mean age (SD; age range)	% females
Young	n = 538	27.1 (SD = 3.95; 20-34)	50.5
Middle age	n= 279	44.0 (SD=5.77; 35-54)	51.0%
Elderly	n= 1218	68.9 (SD=5.07; 60-79)	50.2%
MCI	n= 287	69.7 (SD=4.98; 60-79)	50.2%
AD	n= 272	70.7 (SD = 5.46; 60-79)	50.4%

Table 3. Sequence parameters of the different datasets

Datasets	Sequence parameters

HCP	T1 (3D-MPRAGE), Siemens Skyra, 256 slices, TR=2400 ms, TE=2.14 ms, TI =1000ms, FoV=224x224mm^2, flip angle = 8◦, voxel size = 0.7 x 0.7 x 0.7 mm^3
eNKI	Cross Sectional Lifespan Connectomics and Longitudinal Developmental Connectomics study: T1 (3D-MPRAGE), Tim Trio, 176, TR= 1900 ms, TE = 2.52 ms, TI= 900 ms, FoV = 250 x 250 mm^2, flip angle = 9◦, voxel size = 1 x 1 x 1 mm^3; Neurofeedback study: T1 (3D-MPRAGE), Tim Trio, 192 slices, TR = 2600 ms, TE = 3.02 ms, TI = 900 ms, flip angle = 8◦, voxel size = 1 x 1 x 1 mm^3
CamCAN	T1 (3D-MPRAGE), Tim Trio, 192, TR=2250 ms TE= 2.98 ms, TI= 900 ms, FoV = 256 x 256 mm^2, flip angle = 9◦, voxel size = 1 x 1 x 1 mm^3
1000BRAINS	T1 (3D-MPRAGE), Tim-TRIO, 176 slices, TR = 2.25 s, TE = 3.03 ms, TI = 900ms, FoV = 256 x 256mm^2, flip angle = 9◦, voxel resolution = 1 x 1 x 1mm^3
ADNI	ADNI1: T1 (3D-MPRAGE), TR = 0.65 s, TE = min full, FoV = 256 x 256 mm^2, flip angle = 8◦, voxel resolution = 1.2 mm^3; ADNIGO/2: T1 (3D-MPRAGE), TR = 0.4 s, TE = min full, FoV = 256 x 256 mm^2, flip angle = 11◦, voxel size = 1.2 mm^3; ADNI3: T1 (3D-MPRAGE), TR = 2300 ms, TE = min full echo, TI = 900 ms, FoV = 256 mm, resolution = 1 x 1 x 1mm^3;
OASIS3	T1 (3D-MPRAGE), Tim Trio, TR = 2400 ms, TE = 3.08 ms, TI = 1, FoV = 256 x 256 mm^2, flip angle = 8 ◦, voxel size = 1 x 1 x 1 mm^3

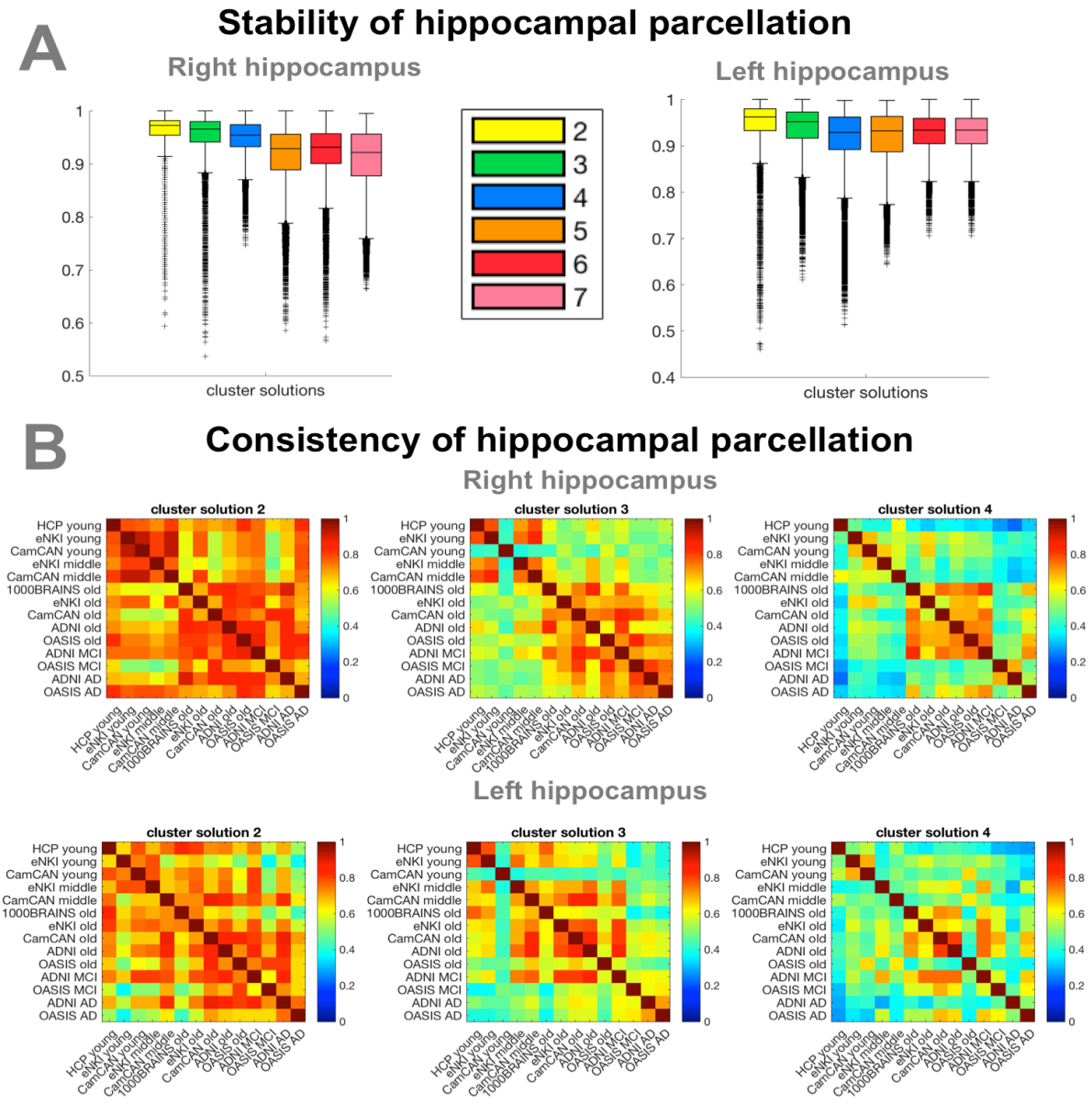


Figure 1. A) Stable organizational patterns were found for right and left hippocampus for cluster solution 2-4 estimated with split-half cross-validation. All clusterings reached very high stability > 0.9 aRI. B) Cross-sample consistency of lower cluster solutions measured with the aRI. Despite overall high stability, the simple parcellation schemes 2-4 were also very consistent > 0.6 across datasets and within age/disease specific groups (e.g. young, elderly) suggesting biological relevance in those differentiations. Cluster solution 3 was exceptionally useful to study age and disease related patterns, because this scheme demonstrated not only high within age/disease similarity but to some extent also across age/diesease groups indicating relatedness, which did not apply for cluster solution 4. In contrast cluster solution 2 showed very high similarity independent of age/disease and dataset suggesting on the one hand a robust biological differentiation, but on the other hand a less

flexible scheme to represent lifespan and pathological alterations. Boxplots with median, 1.5 interquartile range, min. Q1-1.5*IQR, max. Q3+1.5*IQR.

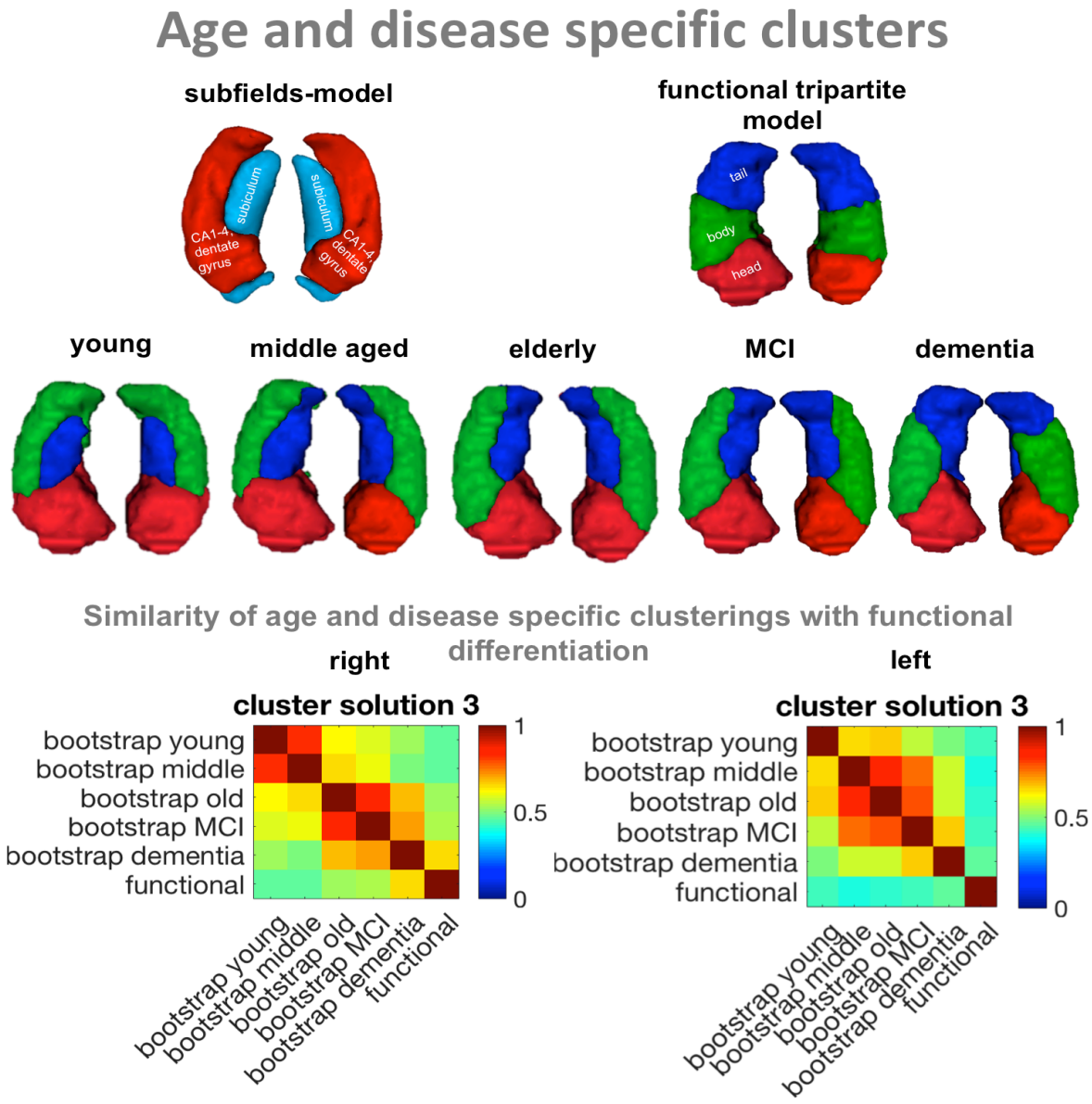
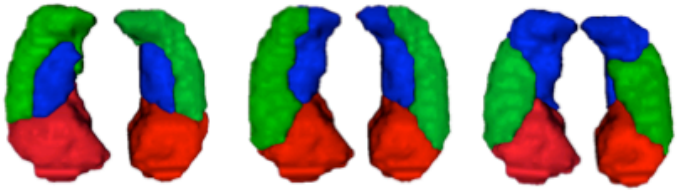


Figure 2. Age and disease specific clusterings of the hippocampus and its similarity to functional differentiation into head, body and tail parcellation. In younger age the hippocampal differentiation was reminiscent of the differentiation between subiculum vs. CA1-4 and dentate gyrus subfields. With increasing age the lateral subregion decreased from the tail, whereas the differentiation in dementia was reminiscent of the functional differentiation into head, body and tail also suggested by the similarity estimation.

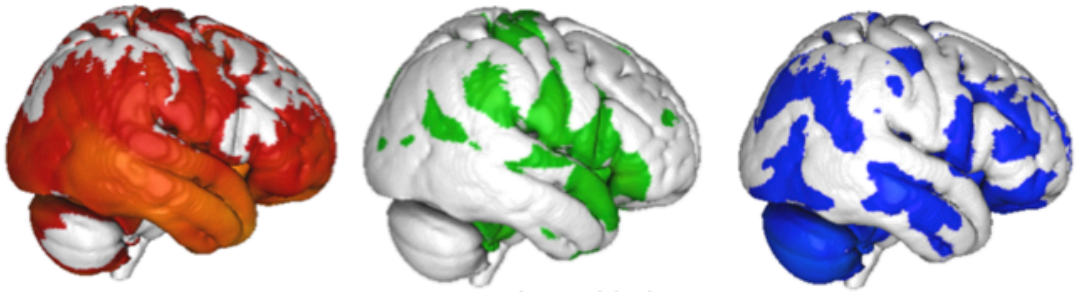
Age and disease specific clusters

young elderly dementia

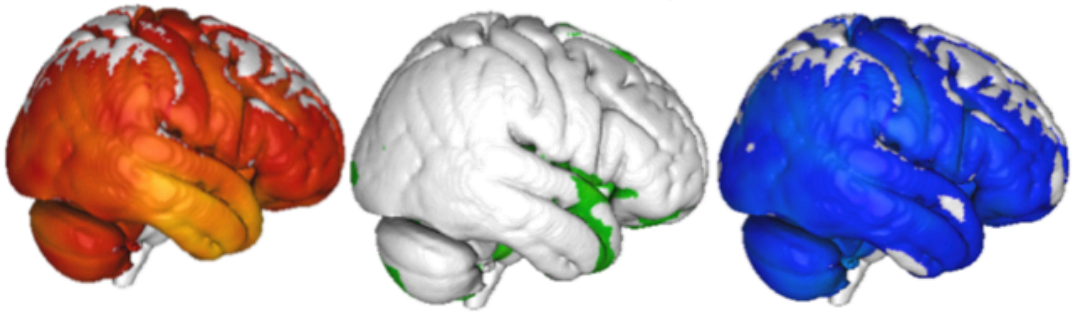


Age and disease specific hippocampus' SC-networks

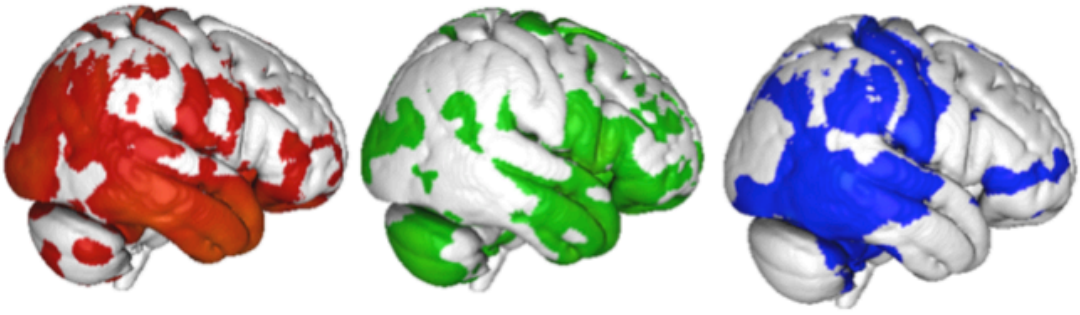
SC-networks in young



SC-networks in elderly



SC-networks in dementia



Functional network in elderly of the SC clusters obtained in dementia

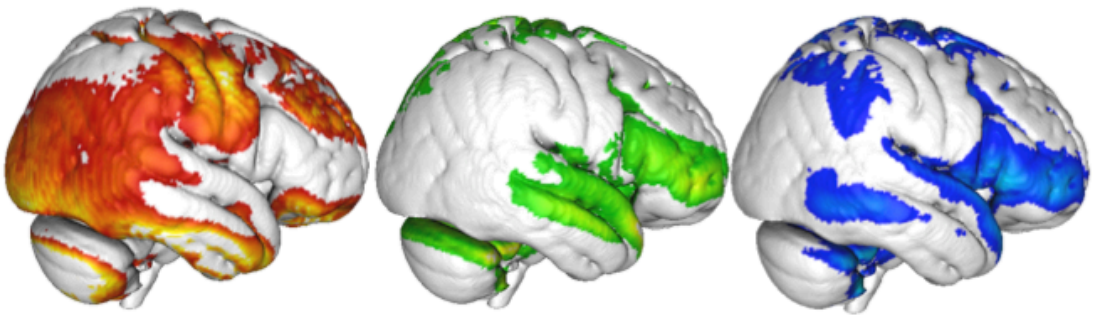


Figure 3. Patterns of structural covariance of each hippocampus' subregions in young, elderly and dementia groups. Relative resting state-functional connectivity networks of dementia-hippocampus in healthy elderly resembled structural co-variation networks of dementia hippocampus in dementia group. Uncorrected ($P < 0.001$), thresholded T=1.

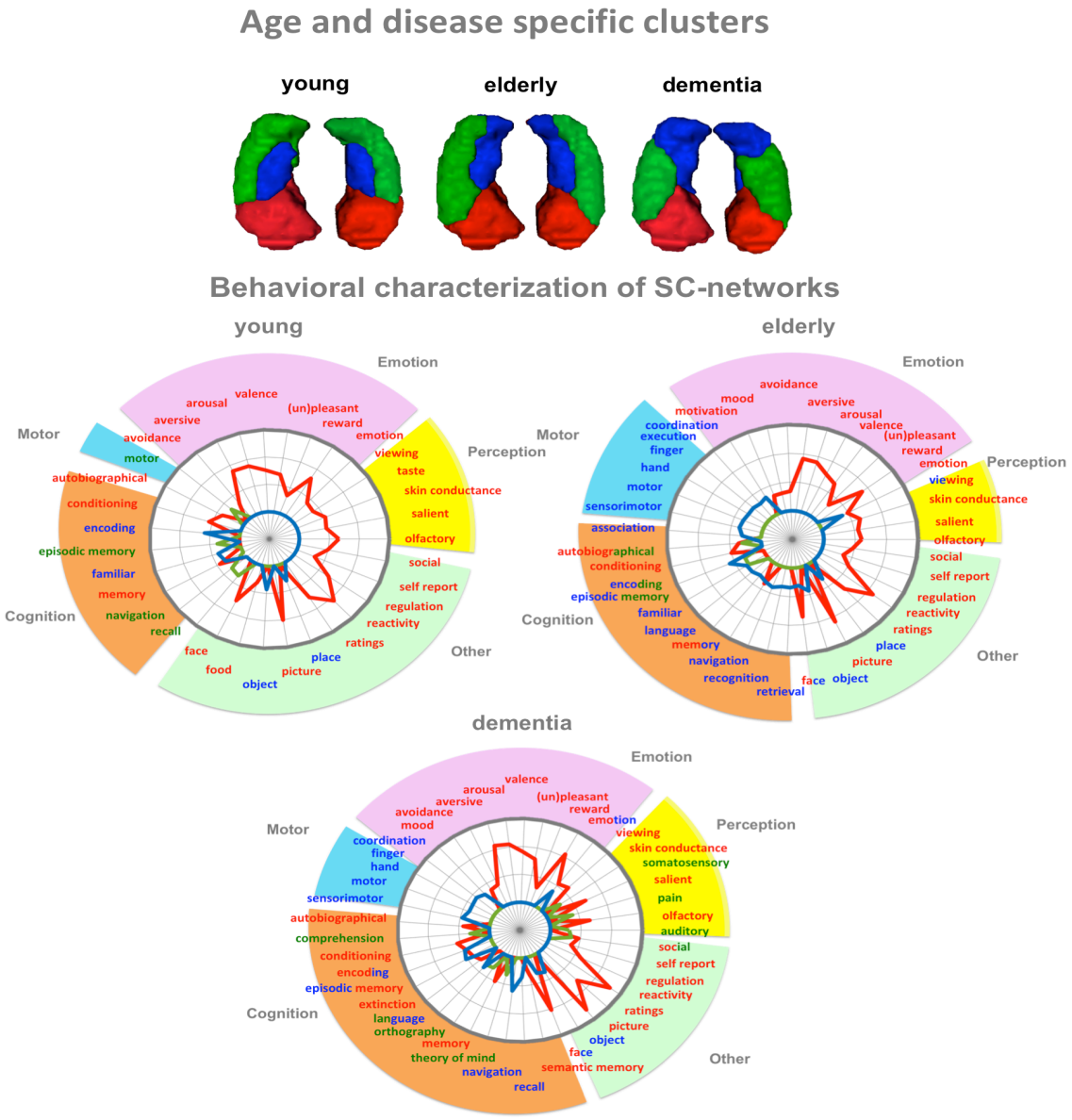


Figure 4. Behavioral characterization of clusters' co-variance network in age and disease groups using NeuroSynth. Behavioral profiles of anterior cluster's co-variance network remained relatively stable across the lifespan and in disease playing a major role in automatic perceptual-emotional approach-behavior in learning, establishing self-related memories. Across the lifespan the medial (blue) subregion's network changed from being associated

with visual processing in younger years to being also motor-related in older age. The lateral-body (green) subregion in the group of dementia was behaviorally associated with language and theory of mind processing while the lateral subregion did not show a clear behavioral specificity in the second half of lifespan compared to the anterior subregion.

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Competing interests

The authors report no competing interests.

Supplemental Material

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