Resting-state network alterations differ between Alzheimer's disease atrophy subtypes

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Abstract

Several Alzheimer's disease (AD) atrophy subtypes were identified, but their brain network properties are unclear.

We analyzed data from two independent datasets, including 166 participants (103 AD/63 controls) from the DELCODE and 151 participants (121 AD/30 controls) from the ADNI cohorts, aiming to identify differences between AD atrophy subtypes in resting-state functional MRI intra-network connectivity (INC) and global and nodal network properties.

Using a data-driven clustering approach, we identified four AD atrophy subtypes with differences in functional connectivity, accompanied by clinical and biomarker alterations, including a medio-temporal-predominant (S-MT), a limbic-predominant (S-L), a diffuse (S-D) and a mild-atrophy subtype (S-MA). S-MT and S-D showed INC reduction in the default mode, dorsal attention, visual and limbic network, and a pronounced reduction of *global efficiency* and decrease of the *clustering coefficient* in parietal and temporal lobes. Despite severe atrophy in limbic areas, the S-L exhibited only marginal global network but substantial nodal network failure. S-MA, in contrast, showed limited impairment in clinical and cognitive scores but pronounced global network failure.

Our results contribute towards a better understanding of heterogeneity in AD with the detection of distinct differences in functional connectivity networks accompanied by CSF biomarker and cognitive differences in AD subtypes.

Introduction

Alzheimer's disease (AD) shows considerable heterogeneity in central disease characteristics among individual patients, who may differ in their cognitive profiles [1] and biomarker patterns [2] . Postmortem studies separating groups with distinguishable atrophy patterns and histopathological features [3, 4] suggest the existence of biologically distinct AD subtypes, supported by evidence from magnetic resonance imaging (MRI), tau positron-emission-tomography (PET)[5] and clinicopathological research [6].

An MRI-based classification of subtypes can be achieved by visual atrophy ratings [7, 8] or data-driven methods [9-13]. Most studies, including those in prodromal disease [14], subdivide AD atrophy patterns into (i) a typical subtype with accentuated pathology of the hippocampus and association cortex; (ii) a limbic predominant subtype with atrophy comprising the limbic system, including the hippocampus; (iii) a hippocampal sparing subtype; and (iv) a minimal atrophy subtype [15]. These AD subtypes differ in their clinical progression rate, neurocognitive scores, years of education, disease duration, genotype and cerebrospinal fluid (CSF) biomarker profiles [14, 15]; further research is warranted to better characterize the underlying pathophysiological differences. To our best knowledge, differences in functional connectivity of resting-state networks between AD subtypes together with neurocognitive and biomarker data have not been explored yet. Furthermore, most previous studies classified patients based on clinical data rather than biomarker information, resulting in heterogeneous datasets. Here we minimized heterogeneity and potential misdiagnoses by using a biomarker-based classification scheme informed by clinical diagnoses [16].

The widespread loss of cortical neuronal connections in AD causes disruptions of brain connectivity [17]. Resting-state functional MRI can quantify the degeneration of the cerebral functional architecture and is widely used to investigate intrinsic large-scale neural

networks [18]. Coherent patterns in spontaneous fluctuations of the blood oxygen level depended (BOLD) signal represent temporarily stable and reproducible intrinsic brain networks, overlapping with individual cognitive and behavioral characteristics [19]. The decline in functional connectivity is associated with disease progression and is found typically in AD in the default mode network (DMN), linked to episodic memory processing [20] and covering hotspots of amyloid-β (Aβ) and tau pathology [21].

Graph theory is a framework used to characterize the behavior of complex brain networks [22]. Connectome-based analyses allow measuring network segregation (i.e. *clustering coefficient*, *modularity* and *transitivity*) and integration (i.e. *global efficiency* and *degree*). *Global efficiency*, *modularity* and *transitivity* relate to large-scale networks, whereas *clustering coefficient* and *degree* characterize network properties at a local level [23, 24]. On a nodal level, highly connected regions, referred to as hub regions, are of primary interest. Regions with a high number of connections can be detected by calculating the *degree* [25]. Previous studies in AD revealed decreased network segregation measures [24] and increased measures of network integration compared to controls [26]. Additionally, *clustering coefficient* and *modularity* are decreased in AD [27].

Recently, differences in structural connectivity [7] and cognitive performance [14] between different AD subtypes have been characterized. However, alterations in functional connectivity remain to be explored. Here, we aimed to explore heterogeneity in network properties in the DMN and other resting-state networks between distinct AD subtypes and to investigate how cognitive and AD biomarker differences are associated with these functional network alterations.

Methods and materials

Data included in this study originate from datasets of two independent study cohorts. The first dataset was obtained from the AD Neuroimaging Initiative (ADNI) launched in October 2004 (ClinicalTrials.gov IDs: NCT02854033, NCT01231971). The second dataset was obtained from the Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE)-Longitudinal Cognitive Impairment and Dementia Study (DELCODE), an observational brain imaging cohort (German Clinical Trials Register: DRKS00007966). Per ADNI and DELCODE protocols, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. Experiments were undertaken with the understanding and written consent of each subject. All local institutional review boards and ethical committees approved the study protocol [28].

Participants

The AD and control groups were defined considering Aβ status and clinical dementia rating (CDR) score. Participants were included based on the availability of T1-weighted structural MRI, resting-state functional MRI and Aβ status information.

The participants in the ADNI dataset were recruited for the ADNI2, ADNI-go and ADNI3 convenience cohorts, details about the general ADNI inclusion and exclusion criteria can be found in the ADNI procedures manual available online (https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). Aβ-positivity in ADNI was defined according to established cut-points as CSF Aβ1-42 concentration<980 pg/mL [29], or 18F-AV-45 or 18F-Florbetaben Aβ-PET normalized composite score with a cutoff>1.11 or>1.08 standardized uptake value ratio (SUVR) respectively [30], resulting in the ADNI dataset of n=160. After quality assessment and preprocessing of the MRI data, n=9 participants did not

meet the predefined image quality criteria (for details section ***MRI preprocessing)*** and were excluded from the subsequent analyses, resulting in a final dataset of n=151 participants (mean age=75 years, 84 females, including n=121 Aβ-positive and clinical dementia rating (CDR)≥0.5 AD patients (mean age=75 years, 63 females) and n=30 Aβ-negative and CDR=0 controls (mean age=77 years, 21 females).

171 participants in the DELCODE dataset met the inclusion criteria. N=5 participants did not meet the predefined image quality criteria and were excluded from all further analyses, resulting in a final cohort of n=166 (mean age=72 years, 93 females). Aβ-positive participants with CSF Aβ1-42<496 pg/ml [31] and CDR≥0.5 were defined as AD (n=103, mean age=74 years, 57 females), whereas Aβ-negative participants were defined as healthy controls (HC) with CSF Aβ1-42>496 pg/ml and CDR=0 (n=63, mean age=69 years, 32 females).

MRI acquisition

The subjects included in the present study were scanned at various sites with 3T MRI scanners manufactured by GE Healthcare (Chicago, Illinois, United States), Philips Medical Systems (Hamburg, Germany) or Siemens Healthineers (Erlangen, Germany). The Alzheimer's Disease Neuroimaging Initiative (ADNI) MRI protocol is reported elsewhere (http://adni.loni.usc.edu/methods/mri-tool/mri-acquisition/). DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) MRI scanning was performed at nine different DZNE imaging sites on Siemens Healthineers 3T MRI scanners, using synchronized acquisition parameters. We included T1-weighted MPRAGE sequences (repetition time (TR), 2500 ms; echo time (TE), 4.37 ms; flip angle (FA), 7 degrees; isotropic voxel size, 1 mm) in our analyses. FMRI imaging was performed using the following parameters: DELCODE: 180 volumes; FoV, 224x224x165 mm; TR, 2580 ms; TE, 30 ms; FA, 80°; isotropic voxel size,

3.5 mm; 7 min 54 s and ADNI: 200 volumes; FoV, 220x220x160mm; TR, 3000 ms; TE, 30; FA=90°; isotropic voxel size: 3,4 mm; 10 min.

MRI preprocessing

Every scan was visually inspected by an experienced radiologist for completeness, cuts, subject motion and other artefacts (e.g., “blurring”, “echoes”, “ghosting”). Following this step, the image was classified as "usable, questionable, unusable". We included only images classified as usable in the analysis.

Brain atrophy was analyzed using FreeSurfer version 6 (http://surfer.nmr.mgh.harvard.edu/). All T1-weighted images were processed in the FreeSurfer segmentation recon-all pipeline [32] Segmentations were visually checked for accuracy and corrected if necessary.

Functional connectivity analysis was performed using the CONN-fMRI Functional Connectivity Toolbox (V17, www.nitrc.org/projects/conn) and SPM 12 (www.fil.ion.ucl.ac.uk/spm/). The default preprocessing pipeline for volume-based analyses was used, comprising realignment, slice-time correction, segmentation and structural and functional normalization, ART-based outlier detection and functional smoothing using a 6 mm kernel (https://web.conn-toolbox.org/fmri-methods/preprocessing-pipeline). Temporal filtering was performed to remove physiological noise. Assessment of motion in both cohorts revealed comparable results (DELCODE: 0.01+-0.12 (79.6% match with null hypothesis; ADNI: 0.02+-0.12 (80.1% match with null hypothesis). (After preprocessing, region-of-interest (ROI)-based intrinsic connectivity was obtained with bivariate correlation matrices in cortical and subcortical ROIs, using the multimodal Brainnetome (BN) atlas [33], registered to the functional image. Correlation coefficients were Fisher-r-to-z-transformed consecutively.

AD atrophy subtype identification

For subtype classification, individual cortical surfaces obtained from each participant's T1-weighted MRI using FreeSurfers recon-all were registered to the FreeSurfer standard subject template (fsaverage6) and resampled to 40,962 vertices for each hemisphere to account for inter-subject variability of brain shapes and size [13]. Subsequent analyses were performed using in-house MATLAB (The MathWorks, Inc.) scripts in both cohorts.

To obtain an atrophy z-score vector, representing the atrophy pattern of each AD subject, the mean cortical thickness value from every vertex in the AD subjects was subtracted from the cortical thickness values of every vertex in the controls divided by the standard deviation in both hemispheres. Atrophy z-score vectors were consecutively concatenated and a similarity matrix of correlation coefficients between the obtained atrophy z-score vectors of any two AD subjects was calculated.

To identify atrophy subtypes in the AD cohorts based on the correlation of atrophy pattern between any two subjects, an unsupervised cluster detection approach using the Louvain community analysis method implemented in the brain connectivity toolbox was applied [34]. This subtyping approach uses the similarity correlation matrix and has previously shown high reproducibility and strong associations with cognitive performance [13]. This unsupervised clustering approach is suggested to be less vulnerable to sampling bias compared to hierarchical clustering approaches. The outcomes in hierarchical clustering tend to cluster based on the overall similarity of the cortical thickness rather than cortical atrophy patterns so that the chosen approach is suggested to be more sensitive to cortical atrophy [13]. Additionally, the approach showed excellent reproducibility and the Louvain method was shown to be suitable for high-dimensional data [35].

To determine the ideal cluster number, we tested three-cluster and four-cluster solutions where four-cluster solutions were generally more suitable to subtypes previously found in

neuroimaging datasets [7, 14, 36], with several studies report four subtypes in a recent review by Ferreira et al. [14, 15].

We modified the approach using a consensus community structure approach to obtain stable results through 1,000 iterations with a correction of individual-level modular decomposition [28]. The level of subtyping can be controlled by the gamma value, a resolution parameter of the Louvain community structure analysis controlling the number of clusters, with a smaller value resulting in a smaller number of subtypes [35]. The gamma value was controlled, obtaining subtyping results equivalent to previous imaging and postmortem studies [3, 6, 14].

Dice overlap

To quantify the overlap of atrophic regions between the two datasets, we compared the regions after setting the threshold level of uncorrected log-p>1.31 ($p<0.05$) on vertex-wise overlay imaging data derived from the statistical comparison with controls. We calculated dice coefficients between atrophy subtypes from both datasets in MATLAB.

Functional connectivity analysis

We analyzed functional connectivity characteristics of the atrophy subtypes in seven cortical intrinsic functional connectivity networks [19]. Within each network, intra-network connectivity (INC) composite score was calculated by averaging the network ROIs (based on the cortical Brainnetome atlas parcellation) functional connectivity Fisher-r-to-z-transformed correlation values [37]. The ROIs with the nodes used for the functional network analysis are presented in **Supplementary Figure 1** and **Supplementary Table 2**. To investigate the global and local network properties and differences between the different subtypes in the resting-state brain networks, we performed a graph theory network analysis. An undirected

network was constructed from the functional connectivity correlation values with subsequent analysis of graph metrics comparing each subtype using permutation-based ANCOVA statistics with Benjamini and Hochberg false discover rate (FDR) correction to control for multiple comparisons in the GraphVar toolbox [38]. The following graph metrics were calculated on a global level: (i) *global transitivity* (referred to as global *clustering coefficient*), (ii) *global efficiency*, (iii) *modularity* using the Louvain method and (iv) *global strength*. On a local level (i) *local efficiency*, (ii) *degree* (iii) *clustering coefficient*, and (iv) *betweenness centrality* were investigated [34]. The visualization of the global and local network properties was obtained using ggplot2 in R (https://www.r-project.org/) and BrainNetViewer [39]. We showed our findings on the median threshold.

Clinical characteristics and CSF biomarkers

The severity of dementia symptoms was quantified using the CDR sum of the boxes (CDR-SoB) score. The cognitive performance was assessed using established cognitive composite scores for memory (MEM) and executive functions (EXEC) in the DELCODE [31] and ADNI [40, 41] datasets. Additionally, the Mini-Mental-State Examination (MMSE) score is reported given its high relevance in everyday clinical practice. CSF biomarkers were assessed in both cohorts using established commercially available analysis kits, following standardized procedures [31]. The CSF concentrations in the ADNI cohort for Aβ-42, p-tau181 was quantified in aliquoted samples, analyzed using the electrochemiluminescence immunoassay (ECLIA) Elecsys on a fully automated Elecsys cobas e 601 instrument (Roche Diagnostics GmbH, Penzberg, Germany) using a single lot of each reagent for each of the 3 measured biomarkers. In the DELCODE cohort, V-PLEX Aβ Peptide Panel 1 (6E10) Kit (K15200E) and V-PLEX Human Total Tau Kit (K151LAE) (Meso Scale Diagnostics LLC, Rockville,

MD, USA) and Innotest Phospho-Tau(181P) (81581; Fujirebio Germany GmbH, Hannover, Germany) were used.

Statistical analysis

Statistical differences between AD atrophy subtype groups and HC in each dataset were tested on cortical z-score maps using two-tailed, two-sample unpaired n=1,000 permutation-based t-tests in FSL-PALM (Permutation Analysis of Linear Models)[42], applying Threshold Free Cluster Enhancement (TFCE) and controlling for family-wise error rate (FWE); additionally, uncorrected contrasts are reported (both $p<0.05$).

SPSS (IBM, v25) and R (https://www.r-project.org/) were used for statistical analyses. Subtype group differences in relevant confounding variables (age, gender, *APOE* genotype and educational years) were compared with Kruskal-Wallis-tests. We detected significant differences in relevant covariates between the subtype groups in the pooled dataset for educational years and gender but not for age or *APOE* genotype. All consequent subtype group comparisons were therefore adjusted for gender and educational years. All fcMRI analyses were adjusted to account for different imaging acquisition sites using several MRI vendors with harmonized protocols in different cohorts. Functional connectivity scores, neurocognitive scores and CSF biomarker scores were compared in the entire cohort as well as between subtypes using Analysis of Covariance (ANCOVA). Post-hoc pairwise comparisons were Bonferroni corrected as appropriate. Results were considered significant at $p<0.05$ (two-tailed). Deviation from normal distribution was assessed by visual inspection of the data distribution and Shapiro-Wilk-test. Deviations from the normality distribution were detected for the functional connectivity and CSF biomarker scores. We transformed these variables into normal scores of ranks using the Rankit`s method [43]. Cognitive composite scores and CSF

biomarkers were z-transformed within each cohort to compare the results independent of the measuring scale.

Comparisons of network properties between the subtypes were performed in the GraphVar Toolbox [38] using non-parametric permutation tests at a range of network thresholds (min=0.1 to max=0.4) with a 0.02 interval. Non-parametric analyses were conducted testing against shuffled data with n=1,000 permutations. A median threshold of 0.24 was used for comparisons of network measures. There is currently a no broader consensus on what threshold should be reported in graph-based analyses [44]. Our decision to report a median threshold was based on the idea to provide the reader with the most representative number as an overview. A random networks/groups FDR correction for multiple permutation comparisons was used at $p<0.05$ (two-tailed) for global and nodal measures at various network densities.

Data Availability Statement

All ADNI data is deposited in a publicly accessible repository and can be accessed at adni.loni.usc.edu. For the DELCODE dataset, anonymized data analyzed in the current study will be made available upon reasonable request from qualified investigators.

Results

Characteristics of the cohorts

The characteristics of the ADNI and DELCODE cohorts are presented in **Table 1**. The AD participants in both cohorts demonstrated comparable sociodemographic and neurocognitive measures, except for years of education, with more years in ADNI. In DELCODE, controls were younger and included a lower proportion of female participants compared to ADNI controls.

Atrophy pattern in AD subtypes

In both datasets (DELCODE and ADNI), similar four subtypes were identified, including (i) a medio-temporal predominant subtype (S-MT); (ii) a limbic predominant subtype (S-L); (iii) a diffuse subtype (S-D); and (iv) a mild atrophy subtype, with relative parahippocampal sparing (S-MA). The differences between the four subtypes within the AD group and compared to the HC are shown in **Figure 1A** for the ADNI dataset and **Figure 1B** for the DELCODE dataset. S-MT showed atrophy mainly in the (medial) temporal lobe, while S-L had an atrophy pattern, including the cingulate cortex and parahippocampal brain areas. In contrast, S-D was associated with a diffuse atrophy pattern, including large areas of the neocortex comprising the parietal lobe. The S-MA subtype was characterized by patchy cortical atrophy with a relatively low degree of parahippocampal atrophy. Importantly, cortical atrophy in each of the four subtypes followed a similar pattern in both datasets, with overall more severe atrophy across all subtypes in DELCODE. The spatial overlap of the atrophy subtypes between the two datasets was evaluated using the dice coefficient (DCE), showing good overlap for S-MT (DCE=0.44), S-L (DCE=0.51) and S-D (DCE=0.64) and less pronounced overlap for S-MA (DCE=0.07), most likely explained by the patchy pattern with less atrophy overall.

Clinical, Cognitive and CSF biomarker differences between the atrophy subtypes

Similar differences in clinical and cognitive scores and CSF biomarkers between the four subtypes were observed in both datasets. Dementia severity measured by CDR was highest in the S-MT and S-D subgroups with lower scores in S-L and S-MA and HC. Concordantly, cognitive performance measured by the MMSE was lowest in S-MT and S-D with higher scores in S-L and S-MA and HC (**Table 2**). Since the atrophy subtypes showed good overlap and similar clinical characteristics across DELCODE and ADNI, we pooled the participants in each sub-group across the datasets for all subsequent analyses as shown before [14].

ANCOVA test revealed significant differences between the subtypes and HC for MEM ($p<0.001$), EXEC ($p<0.001$), CSF t-tau ($p<0.001$) and p-tau181 ($p<0.001$) and Aβ1−42 ($p<0.001$). For MEM, post-hoc pairwise comparisons showed lower z-scores in S-MT and S-D compared to S-L and S-MA and HC. A similar pattern was found for EXEC, with lower z-scores in S-MT and S-D compared to S-L and S-MA and HC. CSF t-tau was higher in S-MT and S-D compared to S-L and S-MA and HC; similar differences were also observed for p-tau181 with higher z-scores in S-MT and S-D compared to S-L and S-MA and HC (**Figure 2A**). *APOE* genotype did not differ between the subtypes. In the comparison between subtypes, hippocampal atrophy was most prominent in S-MT and S-D. Differences in participant's characteristics, cognitive composite, hippocampal volume, and CSF biomarker z-scores between the subtypes are presented in **Table 2**. Independent analysis results for both cohorts are shown in **Supplementary Table 1**.

Intra-network resting-state functional connectivity differences

Following FDR correction for multiple comparisons assessing the INC in seven resting state networks, differences between the subtypes and HC in the DMN ($p=0.035$), LN ($p=0.035$),

dorsal attention network (DAN) (p=0.035) and visual network (VN) (p=0.007) but not in the frontoparietal network (CON) (p=0.28), salience network (SAL) (p=0.18), somatosensory network (SMN) (p=0.89) and were detected using ANCOVA test. Subsequent post-hoc comparisons revealed a higher INC of the DMN in S-L vs. S-MT (p=0.01) and S-L vs. S-D (p<0.001) and S-L vs. S-MA (p<0.02), higher INC in the DAN in HC vs. S-MT (p=0.003), HC vs. S-D (p=0.001) and HC vs. S-MA (p=0.04). In the LN, higher INC was revealed in S-MT vs. S-D (p=0.03) and S-L vs. S-MA (p=0.03) and HC vs. S-MA (p=0.01). In the VN INC was higher in HC vs. S-MT (p<0.001), HC vs. S-D (p=0.001), S-L vs. S-MT (p=0.01) and S-L vs. S-D (p=0.04). Z-score differences between the subtypes and HC in the pooled dataset are presented in **Figure 2B** and **Table 3.** INC differences between HC and subtypes for both cohorts independently are shown in **Supplementary Table 3** and **Supplementary Figure 2**.

AD subtype characteristics in global network analysis

In a graph theory analysis of global network properties on whole-brain level, significant differences between the subtypes in *global efficiency* (p<0.001), *strength* (p<0.001) and *transitivity* (p<0.001), but not in *modularity* (p=0.68) were revealed. On a network level, DMN but not LN showed significant differences between the subtypes for *global efficiency* (p<0.001), *strength* (p<0.001) and *transitivity* (p<0.006), but not *modularity* (p=0.61).

In post-hoc pairwise comparisons on a global level, S-L showed higher *global efficiency* and *transitivity* vs. S-MT, S-D. Both were lower in S-MT than in S-MA. Moreover, S-L exhibit lower *transitivity* vs. S-MA, and S-MT lower *global efficiency* than S-D. *Global strength* was lowest in S-MT and highest in S-L, with S-L significantly higher than S-MT and S-D and S-MA higher than S-MT, but lower than S-L.

Within the DMN, S-L showed the highest *global efficiency* vs. S-MT, S-D and S-MA. *Global efficiency* was higher in S-MA than in S-MT. Additionally, S-L had higher *transitivity* in comparison with S-MT and higher *transitivity* vs. S-D and S-MA. Again, *global strength* was lowest in S-MT and highest in S-L, with S-L significantly higher than S-MT and S-D and S-MA. (**Table 4 and Figure 3**).

AD subtype characteristics in nodal network analysis

Addressing the main research question of this study (i.e., how local changes in network properties of subtypes are related to characteristics of atrophy patterns), we calculated the nodal measures of *betweenness centrality, degree, clustering coefficient* and *local efficiency* on whole-brain level (median threshold=0.24). Differences in *degree* (a measure of integration and one of the most important measures of network structure) are shown in **Figure 3**. The S-L subtype showed a reduced *degree* in the cingulate gyrus vs. S-MT, S-D and S-MA. S-MT exhibited a reduced *degree* in the caudal area of the right parietal and left temporal lobe vs. S-L. *Clustering coefficient* (indicating resilience against random network damage) was reduced in S-MT vs. S-L in multiple ROIs comprising the frontal, temporal, parietal and occipital lobe. A similar pattern, with pronounced changes in lateral temporal and frontal regions, comprising fewer significant ROIs was observed comparing S-D and S-L. S-MA showed reduced *clustering coefficient* in frontal and temporal regions vs. S-L. Significant differences between the subtypes in *clustering coefficient* are shown in **Figure 3**.

To compare the differences of nodal measures within RS networks between the subtypes, we selected the nodes belonging to the DMN, LN and VN, as these networks show significant differences in functional connectivity between the subtypes. Within nodes of the DMN, differences between the subtypes were found for *local efficiency*, comprising multiple

ROIs in the frontal, temporal and parietal lobe as well as cingulate gyrus and precuneus reduced in S-L and S-MA compared to S-MT with a similar pattern in S-L vs. S-D. *Local efficiency* was reduced in the frontal, parietal and temporal lobe, including the precuneus in S-MA vs. S-L. *Clustering coefficient* was significantly lower in S-MT and S-D vs. S-L in the frontal and temporal lobe, the gyrus cinguli and the precuneus. However, *clustering coefficient* in S-L differs with S-MA in the frontal and temporal lobes. *Degree* was lower in the posterior temporal lobe in S-MT vs. S-L and S-MA. *Betweenness centrality* was reduced in the cingulate gyrus in S-L vs. S-MT. Nodes belonging to the LN showed significant reductions in *local efficiency* in the frontal and temporal lobe and the fusiform and parahippocampal gyrus. Nodes belonging to the VN showed in S-MT vs. S-MA reduced local efficiency but increased local efficiency in S-L vs. S-D in several regions. Clustering coefficient was reduced in S-MT vs. S-L, comprising mainly parietal and occipital lobes as well as fusiform, parahippocampal and cingulate gyri; but increased in S-L vs. S-D in parahippocampal and cingulate gyri. Results of nodal graph measures on a network level for the DMN, LN and VN are summarized in **Table 5**.

Discussion

Substantial differences between individual AD patients can exist on clinical, cognitive and biomarker levels. Only recently, the unsupervised classification of atrophy patterns emerged as an approach allowing to distinguish separate AD subtypes with distinct cognitive and biomarker profiles [14]. However, until now, there was no evidence on brain functional network differences between the subtypes, limiting conclusions about their functional relevance. We addressed this key question by analyzing differences in resting-state functional connectivity networks and graph theory-based brain network measures on a global and nodal level. In addition, we explored biomarker and cognitive differences between atrophy subtypes in two independent datasets from the prospective DELCODE and ADNI cohorts.

The main findings of our study are: (i) in line with previous research, using an unsupervised similarity-based clustering algorithm, we identified four distinct subtypes in two independent datasets exhibiting similar brain atrophy patterns as well as clinical and cognitive characteristics; (ii) INC exhibit a heterogeneous alteration pattern for the different subtypes compared among each other and to HC, with district INC reductions in S-MT and S-D and most deviant results in the S-L in most RS networks (iii) the S-MT, S-D and S-MA subtypes showed reduced global *network efficiency* compared to the S-L subtype; (iv) on a nodal level, network analysis revealed reduced *degree* and *clustering coefficient* in regions highly overlapping with the atrophy pattern of the particular subtype; and (v) CSF biomarkers were substantially more pathological in all subgroups compared to HC, among subgroups S-L exhibited the lowest tau elevations. (vii) Cognitive scores were reduced in all subgroups compared to HC, with S-MT and S-D revealing pronounced descent with a lesser degree in LN and S-MA.

To the best of our knowledge, this is the first study to assess functional network connectivity changes between different atrophy subtypes in AD. We report differences

between subtypes for INC in the DMN, VN and the LN. Previous research described the DMN as one of the networks most vulnerable to degeneration in AD [20, 21]. A study comparing multiple imaging biomarkers and intrinsic functional connectivity networks in AD demonstrated substantial overlap between atrophic changes and INC in the anterior LN followed by the DMN [45].

Considering the atrophy pattern, clinical and neurocognitive scores and CSF biomarkers using a two-dimensional framework including typicality and severity, S-MT and S-D can be characterized along the severity dimension, whereas S-L and S-MA appear to be different AD entities along the typicality dimension, exhibiting divergent network features with smaller cognitive differences [15]. The pattern of INC changes between the subtypes accordingly suggests advanced network degeneration within the DMN in S-MT and S-D along the severity dimension. The S-L subtype, however, exhibits the most deviant alteration pattern in INC over several resting-state networks, including the DMN. Compared to healthy controls, an increased INC was detected in the DMN. Interestingly, the S-MA subtype exhibits a decrease of INC in the LN and DAN compared to healthy controls, a distinct elevation of tau biomarkers and hippocampal atrophy despite very limited cortical atrophy and significant but modest cognitive changes. Atrophy patterns and functional connectivity changes are related, but as functional connectivity reflects the correlation of BOLD fluctuations between regions not necessarily directly connected by structural tracts, the resulting changes in functional connectivity are not identical to atrophy, emphasizing the need to study both variables to gain a better characterization of the derived subtypes.

All atrophy subtypes show some limbic involvement in the cortical atrophy pattern when compared to HC, but not when compared to each other. A similar atrophy pattern has been found in a recent publication in prodromal and early AD patients, where limbic involvement was also revealed for all subtypes vs. HC but not when comparing the subtypes

with each other [14]. Limbic structures are reported to be involved in tau pathology early in the disease [46]. In PET studies, severe hypometabolism was reported in AD and MCI patients in a network comprising structures of the limbic system, including hippocampus, thalamus and the posterior cingulate cortex [47]. These findings emphasize the importance of structures of the limbic systems and the associated limbic network system. Interestingly, the limbic atrophy subtype, despite pronounced atrophy in the limbic system, shows higher INC in the DMN and LN compared with HC, suggesting that atrophy is not directly correlated with functional connectivity on the network level. In synopsis with the CSF biomarker results, it appears that the moderate changes in cognition in S-L might be mainly associated with changes in INC and point to a significant impact of network disturbances over neurodegeneration traits in this subtype.

Differences between the four subtypes were consistently present on measures of global network properties. Our results suggest that measures of global network integration, most importantly *global efficiency*, are reduced in the S-MT and S-D subtypes along the severity dimension and strongly associated with cognitive performance, in line with the well-studied disconnection syndrome in AD [48]. Differences in cognitive performance between the subtypes were previously shown [49]. In comparison, the S-L, and to a lesser extent the S-MT, subtypes showed less severe disconnectivity on a global network level in conjunction with pronounced network changes on a nodal level (*degree*), suggesting a more localized underlying network pathology in these subtypes.

Nodal network changes in graph theory analysis showed a noticeable spatial overlap with the characteristic atrophy pattern of the corresponding subtype as measured by *degree*, expressing the number of links connected to a node as a reflection of the importance of a particular node in the network [34]. In contrast, *clustering coefficient*, a measure of the extent of the local density or cliquishness of a network, was mainly reduced on a nodal level in the

S-MT and S-D subtypes, following a typical distribution pattern of neurodegeneration in clinical and prodromal AD [50].

Even though the S-MA subtype exhibits a pattern of sparse atrophy with better cognitive and clinical scores compared to the other subtypes, INC was reduced to a comparable degree as in S-MT and S-D. Additionally, on a nodal level *clustering coefficient* was decreased in frontal and temporal regions, and *local efficiency* was reduced in areas belonging to the DMN. These changes on a local level might reflect ongoing pathological changes in the absence of clinical or neurocognitive symptoms. Compared to S-L, S-MA demonstrates no difference in Aβ but increased CSF t-tau and p-tau levels. Therefore, patients in the S-MA subgroup may have lower cognitive reserve [8] and be more likely to express AD pathology as network disruptions. Previously, the minimal atrophy pattern was shown to be associated with reduced metabolism in the parietal cortex [51] and a higher rate of cerebral amyloid angiopathy [52], causing network disruptions. Consistent with this finding, we observed a locally reduced *local efficiency* in this area, accompanied by network disruption in the DAN and LN. High vulnerability within nodes of the DMN and other brain network regions in structural graph theory analysis in the S-MA subtype was previously demonstrated [7].

Compared with results from the literature, this study did not show differences between subtypes and HC in the DMN. In numbers, S-L showed increased INC, and in contrast to the other subtypes, decreased INC compared to HC. We speculate that It is possible that the results of the comparison in DMN functional connectivity between controls and AD patients might vary depending on the proportion of S-L subtype in a particular cohort. Another factor that needs to be considered is that the selected patients represent a spectrum of AD patients included MCI and AD participants. A recent meta-analysis shows that depending on the clinical disease stage of the disease, hyper- or hypoconnectivity can occur in the DMN [53].

The question of how differences in neuropathology among subtypes affect INC changes depending on the AD stage should be addressed in further research.

There are potential limitations of our study. First, pathological data to verify the clinical diagnoses were not available; however, we selectively included participants in the AD groups of both datasets following a biomarker-based diagnostic scheme including only Aβ-positive individuals with CDR≥0.5, according to the ATN classification system following the recommendations of the NIA-AA Research Framework [16], minimizing heterogeneity and potential misdiagnosis. Second, the dice overlap in the minimal atrophy subtype was comparatively low; this can be partly explained by the low number of vertices with reduced thickness in participants belonging to this group with a high probability of unequal distribution, although the clinical and neurocognitive scores showed high similarity. Third, the atrophy similarity clustering method could detect clinical AD stages rather than distinct subtypes. Indeed, this is likely the case for the S-MA and the S-D subtypes, however, the S-L and the S-MA subtypes exhibit aberrant network properties and CSF biomarker concentrations and are most likely entities along the typicality and not the severity dimension. Future investigations should consider tau PET as an additional imaging parameter to gain important information about spatial associations between tau distribution and network degeneration particularly in the S-MA subtype. Finally, the controls in the DELCODE dataset were younger compared to the AD patients, which may have resulted in more severe atrophy measures in this cohort; however, it is unlikely that this difference affected the resulting atrophy patterns and therefore the main results of the study.

In conclusion, we demonstrate a robust detection of different AD subtypes using a similarity-based clustering approach. These subtypes show distinct differences in functional connectivity networks and network properties on the local and global levels, accompanied by CSF biomarker and cognitive differences. Our study contributes toward a better

understanding of heterogeneity in AD, with important ramifications for a more individualized approach to diagnosis and treatment. A better characterization of the heterogeneity of functional connectivity changes in AD subtypes lays the foundation for advanced neuromodulatory non-invasive brain stimulation, pharmacological treatment or tailored cognitive interventions aimed at modifying functional connectivity networks. Known differences in patterns of network degeneration may lead to a better-informed, individualized treatment strategy. Follow-up studies should address the longitudinal consequences of the identified heterogeneity.

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Tables

Table 1. Characteristics of the two study cohorts (ADNI and DELCODE). aKruskal-Wallis-test; bChi-squared-test; p-value of differences between the AD groups in both datasets. cMissing data for n=4 participants. dMissing data for n=1 participant.

	DELCODE		**ADNI**			
	AD (N=103)	**HC (N=63)**	**AD (N=121)**	**HC (N=30)**	**p between AD groups**	**p between HC groups**
Age, mean (SD)	74 (6)	69 (5)	75 (8)	77 (8)	0.33[a]	<0.001[a]
Sex, no. female %, (SD)	57 (55)	32 (49)	63 (52)	21 (70)	0.72[b]	<0.001[b]
Years of education, mean (SD)	14 (3)	14 (3)	16 (2)	16 (3)	<0.001[a]	0.07[a]
MMSE, mean (SD)	26 (3)	29 (1)	25 (4)	29 (1)[d]	0.36[a]	0.06[a]
CDR-SoB, mean (SD)	2.7 (2.2)	0	3.2 (2.6)	0	0.06[a]	1[a]
APOE, no. (%) ε4 allele carrier (SD)	66 (64)[d]	9 (14)	68 (56)[c]	6 (21)	0.39[b]	0.64[b]

Abbreviations: AD, Alzheimer's disease; HC, healthy controls; CDR-SoB, Clinical Dementia Rating Sum of the Boxes; MMSE, Mini Mental State Examination; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein ε4 genotype.

Table 2. Differences in sociodemographic characteristics, *APOE* genotype, Alzheimer's disease severity, cognitive performance and CSF biomarker levels between the atrophy subtypes in the pooled dataset. Analysis of covariance with adjustments for age, sex, sites, *APOE* genotype and years of education, post-hoc pairwise comparisons Bonferroni corrected; [d]Chi-squared test; [e]Analysis of covariance with adjustments for age, sex, *APOE* genotype, sites and years of education; [f] CSF biomarker data in n=19 participants were missing (n=8 in S-MT, n=3 in S-L, n=6 in S-D, and n=2 in S-MA). *Significant difference p<0.05 in post-hoc tests.

	HC (n=93)	**S-MT (n=57)**	**S-L (n=41)**	**S-D (n=78)**	**S-MA (n=48)**	**p-value (overall)**	**S-MT vs. HC**	**S-L vs. HC**	**S-D vs. HC**	**S-MA vs. HC**	**S-MT vs. S-L**	**S-MT vs. S-D**	**S-MT vs. S-MA**	**S-L vs. S-D**	**S-L vs. S-MA**	**S-D vs. S-MA**
							Post hoc comparison p-value									
Age, mean (SD)[b]	72 (7)	73 (8)	75 (6)	75 (6)	74 (7)	0.01	0.54	0.02*	0.01*	0.06	0.3	0.17	0.5	0.7	0.56	0.9
Sex, no. female (%)[c]	53 (57)	40 (70.2)	18 (43.9)	39 (50)	23 (47.9)	0.052	-	-	-	-	-	-	-	-	-	-
Years of education, mean (SD)[b]	15 (3)	14 (3)	15 (3)	15 (3)	16 (3)	<0.001	0.01*	0.45	0.47	0.01*	0.5	0.2	<0.001*	0.6	0.002*	0.002*
APOE, no. (%)[c] ε4 allele carrier[a]	15 (16)	32 (60)	21 (53)	50 (64)	31 (65)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.41	0.65	0.65	0.19	0.22	0.95
CDR-SoB, mean (SD)[e]	0 (0)	3.39 (3.02)	2.1 (1.78)	3.66 (2.46)	2.02 (1.52)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.11	0.01*	0.12	0.01*	0.93	0.01*
MMSE, mean (SD)[e]	29 (1)	24.84 (4.3)	26.95 (2.65)	24.44 (4.35)	27.48 (2.44)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.03*	0.71	0.002*	0.01*	0.4	<0.001*
CSF Aβ1−42, z-score[f] (SD)[e]	0 (1)	-2.19 (0.42)	-2.09 (0.47)	-2.11 (0.40)	-2.00 (0.52)	<0.001	<0.001*	<0.001*	<0.001*	<0.001*	0.51	0.4	0.18	0.93	0.5	0.49

CSF p-tau181, z-score[f] (SD)[e]	0 (1)	3.28 (2.96)	1.23 (2.17)	4.50 (3.96)	4.40 (5.01)	<0.001	<0.001*	0.02*	<0.001*	<0.001*	0.01*	0.06	0.37	<0.001*	<0.001*	0.4
CSF t-tau, z-score[f] (SD)[e]	0 (1)	2.83 (2.67)	1.57 (2.44)	4.49 (4.13)	4.22 (4.76)	<0.001*	0.001*	0.09	<0.001*	<0.001*	0.11	0.01*	0.21	<0.001*	0.01*	0.25
Mean Hippocampal volume, z-score (SD)[e]	0 (1)	-0.90 (1.98)	0.24 (2.10)	-0.48 (2.05)	-0.78 (1.25)	0.001*	0.03*	0.32	0.12	0.001*	0.01*	0.47	0.24	0.02*	<0.001*	0.047*
MEM, z-score (SD)[e]	0 (1)	-4.22 (2.29)	-2.76 (1.85)	-3.75 (2.17)	-1.56 (1.68)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.16	<0.001*	0.01*	0.3	<0.001*
EXEC, z-score (SD)[e]	0 (1)	-2.94 (1.75)	-2.19 (1.54)	-2.83 (1.71)	-1.11 (1.51)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.02*	0.94	<0.001*	0.01*	0.01*	<0.001

Abbreviations: HC, healthy controls; S-MT, medio-temporal predominant subtype; S-L, limbic predominant subtype; S-D, diffuse subtype; S-MA, mild atrophy subtype; CDR-SoB, Clinical Dementia Rating Sum of the Boxes; MMSE, Mini Mental State Examination; MEM, composite score for memory domain; EXEC, composite score for executive function domain; CSF, Cerebrospinal fluid; Aβ, amyloid β; p-tau, phosphorylated-tau; t-tau, total-tau; *APOE*, apolipoprotein ε4 genotype.

Table 3. Adjusted group means of intra-network connectivity scores of the pooled dataset. ¥p<0.05 in Analysis of covariance -with adjustments for age, sex, *APOE* genotype and years of education - between any atrophy subgroup DELCODE vs ADNI.

RSN	HC	S-MT	S-L	S-D	S-MA			S-MT vs. HC	S-L vs. HC	S-D vs. HC	S-MA vs. HC	S-MT vs. S-L	S-MT vs. S-D	S-MT vs. S-MA	S-L vs. S-D	S-L vs. S-MA	S-D vs. S-MA
	Mean (SE)					P (overall)	P FDR corrected	P post hoc comparisons									
DMN	-0.01 (0.11)	-0.18 (0.14)	0.38 (0.16)	-0.27 (0.12)	-0.12 (0.15)	0.02*	0.035*	0.36	0.054	0.11	0.57	0.01*	0.58	0.78	<0.001*	0.02*	0.40
DAN	0.01 (0.12)	-0.58 (0.15)	-0.37 (0.17)	-0.58 (0.12)¥	-0.42 (0.16)	0.01*	0.035*	0.003*	0.07	0.001*	0.04*	0.36	1.00	0.48	0.32	0.83	0.43
CON	-0.06 (0.12)	-0.24 (0.15)	0.25 (0.17)	-0.16 (0.12)	-0.09 (0.16)	0.24	0.28	0.33	0.15	0.55	0.88	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
SAL	-0.02 (0.14)	0.12 (0.18)	0.53 (0.20)	0.13 (0.15)	0.47 (0.19)	0.13	0.18	0.57	0.03*	0.51	0.05	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
LN	-0.04 (0.10)	-0.10 (0.13)	0.07 (0.15)	-0.32 (0.11)	-0.52 (0.14)	0.02*	0.035*	0.76	0.53	0.08	0.01*	0.18	0.03*	0.53	0.40	0.03*	0.25
VN	0.02 (0.12)	-0.74 (0.14)	-0.14 (0.16)	-0.55 (0.12)	-0.32 (0.15)¥	<0.001*	0.007*	<0.001*	0.41	0.001*	0.08	0.01*	0.30	0.05	0.04*	0.42	0.24
SMN	-0.06 (0.10)	-0.02 (0.13)	-0.03 (0.15)	0.04 (0.11)	-0.13 (0.14)	0.89	0.89	0.78	0.84	0.49	0.72	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Abbreviations: RSN, Resting-state Network; DMN: Default-mode network, DAN, dorsal attention network; CON, frontoparietal network; SAL, salience network; LN: Limbic network; VN, visual network; SMN, sensorimotor network; HC, healthy controls; S-MT, medio-temporal predominant subtype; S-L, limbic predominant subtype; S-D, diffuse subtype; S-MA, mild atrophy subtype *two-tailed p<0.05.

Table 4. Adjusted group means of graph theory derived global network properties on a whole brain level and within the default mode network, the limbic network, and visual network.

Group means		S-MT	S-L	S-D	S-MA	P (overall)	S-MT vs. S-L	S-MT vs. S-D	S-MT vs. S-MA	S-L vs. S-D	S-L vs. S-MA	S-D vs. S-MA
Global network	Efficiency	0.23	0.26	0.24	0.25	<0.001*	<0.001*	0.02*	<0.001*	<0.001*	0.06	0.1
	Modularity	0.4	0.4	0.4	0.4	0.68	-	-	-	-	-	-
	Strength	5266	6130	5541	5745	<0.001*	<0.001*	0.05	0.002*	0.001*	0.03*	0.18
	Transitivity	0.21	0.25	0.22	0.23	<0.001*	<0.001*	0.11	0.04*	<0.001*	0.01*	0.46
Within default mode network	Efficiency	0.3	0.34	0.31	0.32	<0.001*	<0.001*	0.17	0.02*	0.001*	0.03*	0.21
	Modularity	0.31	0.29	0.31	0.31	0.61	-	-	-	-	-	-
	Strength	199	225	203	207	<0.001*	<0.001*	0.41	0.24	<0.001*	0.006*	0.56
	Transitivity	0.46	0.52	0.47	0.47	0.006*	0.004*	0.84	0.74	0.001*	0.001*	0.86
Within limbic network	Efficiency	0.21	0.22	0.21	0.21	0.25	-	-	-	-	-	-
	Modularity	0.37	0.36	0.38	0.37	0.30	-	-	-	-	-	-
	Strength	68	73	68	65	0.12	-	-	-	-	-	-
	Transitivity	0.25	0.27	0.24	0.22	0.14	-	-	-	-	-	-
Within visual network	Efficiency	0.28	0.31	0.3	0.35	0.08	-	-	-	-	-	-
	Modularity	0.33	0.34	0.33	0.3	0.28	-	-	-	-	-	-
	Strength	160	175	172	167	0.16	-	-	-	-	-	-
	Transitivity	0.39	0.43	0.42	0.4	0.33	-	-	-	-	-	-

Abbreviations: S-MT, medio-temporal predominant subtype; S-L, limbic predominant subtype; S-D, diffuse subtype; S-MA, mild atrophy subtype; *two-tailed permutation-based FDR-corrected $p<0.05$.

Table 5. Summary of changes in nodal topography in regions of interest (ROIs) associated with the default mode network (top) and limbic network (bottom) at a median threshold of 0.24. Permutation FDR p<0.05 (two-tailed).

	Betweenness centrality	**Degree**	**Clustering coefficient**	**Local Efficiency**
DMN				
S-MT vs. S-L	CG ↑	pSTS ↓	SFG, MFG, IFG, OrG, STG, MTG, ITG, PCun, CG ↓	SFG, MFG, IFG, OrG, STG, MTG, ITG, pSTS,IPL, PCun, CG ↓
S-MT vs. S-D	-	-	-	
S-MT vs. S-MA	-	-	-	IFG, OrG, STG, MTG, pSTS, IPL, CG ↑
S-L vs. S-D	-	-	SFG, IFG, OrG, MTG, ITG, PCun, CG ↑	SFG, MFG, IFG, OrG, STG, MTG, ITG, pSTS, IPL, PCun, CG ↑
S-L vs. S-MA	-	-	SFG, OrG, MTG, ITG ↑	SFG, IFG, OrG, MTG, ITG, PCun ↑
S-D vs. S-MA	-	-	-	-
LN				
S-MT vs. S-L	-	-	MFG, OrG, ITG ↓	MFG, OrG, STG, ITG, FuG, PhG ↓
S-MT vs. S-D	-	-	-	-
S-MT vs. S-MA	-	-	-	STG, ITG, PhG ↓
S-L vs. S-D	-	-	MFG, OrG, ITG ↑	MFG, OrG, STG, ITG, FuG, PhG ↑
S-L vs. S-MA	-	-	-	-
S-D vs. S-MA	-	-	-	-
VN				
S-MT vs. S-L	-	-	FuG, PhG, IPL, CG, LOcC ↓	-
S-MT vs. S-D	-	-	-	-
S-MT vs. S-MA	-	-	-	FuG, PhG, IPL, CG, MVOcC, LOcC ↓
S-L vs. S-D	-	-	PhG, CG ↑	FuG, PhG, IPL, PCun, CG, MVOcC, LOcC ↑
S-L vs. S-MA	-	-	-	-
S-D vs. S-MA	-	-	-	-

Abbreviations: S-MT-S-MA, Subtype 1-4; DMN, Default Mode Network; LN, Limbic Network; VN, visual network; SFG, Superior Frontal Gyrus; MFG, Medial Frontal Gyrus; IFG, Inferior Frontal Gyrus; OrG, Orbitofrontal Gyrus; STG, Superior Temporal Gyrus; MTG, Medial Temporal Gyrus; ITG, Inferior Temporal Gyrus; pSTS, posterior Superior Temporal Sulcus; PCun, Precuneus; CG, Cingulate Gyrus; FuG, Fusiform Gyrus; PhG, Parahippocampal Gyrus IPL, Inferior Parietal Lobule; MVOcC, Medial Ventral Occipital Cortex; LOcC, Lateral Occipital Cortex.

Figure legends

Figure. 1. Atrophy regions in Alzheimer's disease subtypes vs. healthy control subjects across atrophy subtypes in the ADNI (A) and DELCODE (B) dataset. *uncorrected $p<0.05$; **FWE-corrected $p<0.05$.

Abbreviations: S-MT, medio-temporal predominant subtype; S-L, limbic predominant subtype; S-D, diffuse subtype; S-MA, mild atrophy subtype.

Figure 2. A) Boxplots of the mean cognitive composite and cerebrospinal fluid biomarker normalized scores +/- 95% confidence interval (CI) (in z-scores). B) Spider plot of the estimated mean z-scores of intra-network connectivity in the resting-state networks. Z-scores of the healthy controls are shown for comparison. Lines show significantly differing subgroups in post-hoc tests when two-tailed-$p<0.05$. Abbreviations: MEM, memory composite score; EXEC, executive functioning composite score; Aβ42, amyloid-β42; tTau; total tau; pTau; phosphorylated tau; INC, intrinsic network connectivity; DMN: Default-mode network, DAN, dorsal attention network; CON, frontoparietal network; SAL, salience network; LN: Limbic network; VN, visual network; SMN, sensorimotor network; HC, healthy controls; S-MT, medio-temporal predominant subtype; S-L, limbic predominant subtype; S-D, diffuse subtype; S-MA, mild atrophy subtype; Sig., Significant; *p (overall)<0.05.

Figure 3. Differences between subtypes in *degree* and *clustering coefficient* in Brainnetome atlas derived regions of interest. Permutation based FDR-corrected two-tailed $p<0.05$ are shown.

Abbreviations: S-M, medio-temporal predominant subtype; S-L, limbic predominant subtype; S-D, diffuse subtype; S-MA, mild atrophy subtype.