Segregation of functional networks is associated with cognitive resilience in Alzheimer's disease.

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ABSTRACT

Cognitive resilience is an important modulating factor of cognitive decline in Alzheimer's disease, but the functional brain mechanisms that support cognitive resilience remain elusive. Given previous findings in normal aging, we tested the hypothesis that higher segregation of the brain's connectome into distinct functional networks represents a functional mechanism underlying cognitive resilience in Alzheimer's disease. Using resting-state functional MRI, we assessed both resting-state-fMRI global system segregation, i.e. the balance of between-network to within-network connectivity, and the alternate index of modularity *Q* as predictors of cognitive resilience. We included two independent samples for validation, including i) 108 individuals with autosomal dominantly inherited Alzheimer's disease and 71 non-carrier controls and ii) 156 amyloid-PET positive subjects across the spectrum of sporadic Alzheimer's disease as well as 184 amyloid-negative controls. In the autosomal dominant Alzheimer's disease sample, disease severity was assessed by estimated years from symptom onset. In the sporadic Alzheimer's sample, disease stage was assessed by temporal-lobe tau-PET (i.e. Braak stage I & III regions). In both samples, we tested whether the effect of disease severity on cognition was attenuated at higher levels of functional network segregation. For autosomal dominant Alzheimer's disease, we found higher fMRI-assessed system segregation to be associated with an attenuated effect of estimated years from symptom onset on global cognition ($p=0.007$). Similarly, for sporadic Alzheimer's disease patients, higher fMRI-assessed system segregation was associated with less decrement in global cognition ($p = 0.001$) and episodic memory ($p=0.004$) per unit increase of tau-PET. Confirmatory analyses using the alternate index of modularity *Q* revealed consistent results. In conclusion, higher segregation of functional connections into distinct large-scale networks supports cognitive resilience in Alzheimer's disease.

INTRODUCTION

Cognitive resilience (CR) is defined as the ability to maintain cognitive abilities relatively well in the presence of age-related brain decline or brain pathologies (Cabeza *et al.*, 2018; Stern *et al.*, 2018a). In Alzheimer's disease (AD), the level of cognitive impairment shows substantial variability even when accounting for key pathologies including beta-amyloid (Aβ) and pathologic tau (Jack *et al.*, 2013; Franzmeier *et al.*, 2020). Protective environmental factors such as education, mid-life activities and physical activity have been found to be associated with lower cognitive impairment and dementia risk in AD (Wang *et al.*, 2017; Chan *et al.*, 2018a; Dekhtyar *et al.*, 2019), suggesting that CR may modulate the impact of pathology on cognition. However, the functional brain properties underlying CR remain elusive. Answering that question may help identify and target brain mechanisms that slow down cognitive decline in the presence of AD pathology. Enhancing CR to delay the onset of dementia as much as by one year would translate into an age-dependent decrease in dementia prevalence of over 10% (Zissimopoulos *et al.*, 2014).

Previous neuroimaging studies have reported several brain features associated with CR in AD (Ewers, 2020), including higher functional connectivity of hubs in the cognitive control and salience network (Benson *et al.*, 2018; Franzmeier *et al.*, 2018a; Neitzel *et al.*, 2019b) or higher glucose metabolism and brain activation of the anterior cingulate and temporal cortex (Stern *et al.*, 2018b; Arenaza-Urquijo *et al.*, 2019; van Loenhoud *et al.*, 2020). These findings provide valuable insight into particular brain regions contributing to CR in AD, but overall those regional findings are diverse and variable across studies (Ewers, 2020). There is currently a lack of understanding of which differences in the global functional brain topology support CR. From a clinical point of view, a single easily accessible measure of global brain function linked to CR would be attractive as a mechanistic functional marker of CR (Medaglia *et al.*, 2017). Here we propose resting-state-fMRI assessed segregation between functional networks (called systems) as a putative neural substrate of CR. The brain is composed of intrinsically wired

functional networks (Smith *et al.*, 2009; Crossley *et al.*, 2013), where each network corresponds to a set of tightly connected regions (Smith *et al.*, 2009; Cole *et al.*, 2014). Such a modular functional organization of the brain in the form of clearly segregated functional networks is critical feature of the functional connectome underlying cognitive performance (Achard *et al.*, 2006; Bullmore and Sporns, 2012; Sporns and Betzel, 2016). Multiple graph theoretical indices have been proposed to quantify the segregation of networks (Sporns, 2018). Here, we focus on the statistic *system segregation* (SyS) which quantifies the extent to which major functional networks are segregated from each other (i.e. high within-network but low between-network connectivity)(Chan *et al.*, 2014). An alternative index is the modularity statistic *Q*, which quantifies extent the clustering of connections into networks from that expected in a randomly connected brain (Sporns and Betzel, 2016). We chose SyS as our primary predictor, given that SyS is best suited to quantify the segregation between pre-defined major resting state networks and thus allows for a clear reference to previously well characterized functional networks (Wig, 2017). Results from resting-state fMRI studies showed that higher SyS was associated with higher global cognitive performance across the adult life span (Chan *et al.*, 2014; Varangis *et al.*, 2019). Few studies have assessed SyS in relation to CR. The proxy measure of CR including higher socioeconomic status (Marden *et al.*, 2017; Chapko *et al.*, 2018) was previously found to be associated with higher SyS in normal aging (Chan *et al.*, 2018b), and in persons with brain injury, higher SyS was associated with better post-recovery cognitive performance (Arnemann *et al.*, 2015), suggesting higher resilience to the impact of brain pathology on cognitive function. Despite these previous findings, to our knowledge no study has yet assessed SyS as a substrate of CR in AD. Here we tested whether higher resting-state fMRI-assessed SyS attenuates the association between markers of AD severity and cognitive decline in two different samples of individuals with genetic or biomarker evidence of AD. In order to enhance criterion validity of our analyses, we also tested the alternate modularity index *Q* as a predictor of CR.

METHODS

Participants

Dominantly Inherited Alzheimer Network (DIAN)

108 carriers of autosomal dominant AD (ADAD) disease-causing mutations in genes *PSEN1,* and *PSEN2* or *APP,* and 71 non-carrier siblings were included from DIAN data freeze 10 (Moulder *et al.*, 2013). Beyond DIAN inclusion criteria, the current study required availability of 3T resting-state fMRI, T1-structural MRI and cognitive assessments. No selection bias (i.e. demographic differences between the included participants and excluded participants) were found ($p>0.05$) for age, gender or education. As a proxy of AD disease severity, we applied the estimated years from symptom onset (EYO), defined as the difference between a participants age at examination and the parental age of symptom onset for ADAD mutation carriers, as described previously (Bateman *et al.*, 2012; Suarez-Calvet *et al.*, 2016; Franzmeier *et al.*, 2018b). We did not use biomarker levels of pathologic tau (as we did in ADNI, see below), since neither cerebrospinal fluid biomarkers of tau nor tau PET were available in all subjects in DIAN. Each participant provided written informed consent. Local ethical approval was obtained at each DIAN site.

Alzheimer's Disease Neuroimaging Initiative (ADNI) -

For the evaluation of late onset AD (LOAD), we included data from the 340 participants included in ADNI phase 3, which were selected based on availability of T1-weighted and resting-state fMRI, ^{18}F-AV1451 tau-PET for the assessment of tau and ^{18}F-AV45 amyloid-PET for the assessment of amyloid deposition. All measures had to be obtained at the same study visit. Using Freesurfer-derived global amyloid-PET SUVR scores normalized to the whole cerebellum (provided by the ADNI-PET Core), all participants were characterized as Aβ+ or Aβ- based on an established cut-point (global AV45 SUVR > 1.11) (Landau *et al.*, 2012). As a control group, we included 184 cognitively normal (CN, MMSE>24, CDR=0, non-depressed)

Aβ- participants. To cover the Alzheimer's continuum, we included 89 CN-Aβ+, 59 mild cognitively impaired (MCI) Aβ+ participants (MMSE>24, CDR=0.5, objective memory-loss on the education adjusted Wechsler Memory Scale II, preserved activities of daily living) and 8 Aβ+ patients with dementia (MMSE<26, CDR>0.5, fulfillment of NINCDS/ADRDA criteria for probable AD) (Petersen *et al.*, 2010). Region of interest (ROI)-specific AV1451 tau-PET data for Freesurfer-based Desikan-Killiany ROIs provided by the ADNI PET-Core has been downloaded from the online ADNI image archive (https://ida.loni.usc.edu). As a proxy of disease severity in sporadic AD, tau-PET uptake averaged across Braak-stage ROI I and III was assessed according to a previously described protocol (Scholl *et al.*, 2016). We specifically focused on these early Braak-stage ROI to enhance sensitivity to tau accumulation during the early stages of AD given that in DIAN mutation carriers include also those over 20 years prior to estimated symptom onset. We excluded the hippocampus (i.e. Braak-stage-II ROI) due to known susceptibility of AV1451 PET PET measures in the hippocampal region to spill-over effects of AV1451 binding in the neighboring choroid plexus (Ikonomovic *et al.*, 2016). Ethical approval was obtained by the ADNI investigators, all participants provided written informed consent.

Neuropsychology

In DIAN, we used pre-established z-score composite scores of global cognition, which was designed by the DIAN cognitive core based on the tests' low ceiling/floor effects, high face validity and sensitivity to early AD, and is included as the primary endpoint in the DIAN clinical trial (Bateman *et al.*, 2017). For the assessment of episodic memory, a memory composite was generated, which was defined as the average z-score (i.e. normalized the full DIAN baseline sample of cognitively normal non-mutation carriers) across all memory scores available in DIAN (i.e. Wechsler Memory Scale-Revised, Story A logical memory immediate and delayed recall; Immediate and delayed recall of a 16-item word list; and an associative

memory test). These tests were chosen due to their sensitivity to changes in early stage ADAD subjects (at clinical dementia raging (CDR) score = 0.05) as previously described (Storandt *et al.*, 2014). For ADNI participants, we used the total score of the ADAS13 for global cognition and the pre-established composite memory score ADNI-MEM (Crane *et al.*, 2012), which are widely used composite scores of cognition in ADNI (Weiner *et al.*, 2017) and thus offer high comparability between studies. As expected, measures of global cognition and memory were correlated within each cohort (DIAN: $r=0.81$, $p<0.001$; ADNI: $r=-0.85$, $p<0.001$).

MRI acquisition and preprocessing

In all samples, MRI data was obtained on 3T scanner systems. Structural MRI was obtained in both samples using a 3D T1-weighted MPRAGE sequence (ADNI: 1 mm isotropic voxel-size, TR = 2300 ms.; DIAN 1.1x1.1x1.2mm voxel-size, TR=2300ms). In ADNI, 200 resting-state fMRI volumes were obtained using a T2*-weighted EPI sequence with 3.4 mm isotropic voxel resolution with a TR/TE/flip angle = 3000ms/30ms/90°. In DIAN, 140 resting-state fMRI volumes were collected also using aT2*-weighted EPI sequence with a TR/TE/flip angle=2230ms/30ms/80°. All resting-state fMRI images were preprocessed and spatially normalized using the same SPM12-based (Wellcome Trust Centre for Neuroimaging, University College London) pipeline using DARTEL as described previously (Franzmeier *et al.*, 2017a; Franzmeier *et al.*, 2017b; Franzmeier *et al.*, 2018b). Resting-state fMRI preprocessing further included motion correction, detrending, band-pass filtering (0.01-0.08Hz), nuisance regression (i.e. 6 motion parameters, mean signal extracted from cerebrospinal fluid and white matter masks), motion scrubbing and spatial smoothing using an 8mm full-width at half maximum gaussian kernel. Motion scrubbing followed a pre-established approach, where we computed frame-wise displacement between adjacent fMRI volumes. Volumes that exceeded a frame-wise displacement threshold >0.5mm were censored (i.e. replaced with zero-padded volumes) together with one preceding and two subsequent volumes.

No subjects were included for which >30% of the resting-state scan had to be removed during motion scrubbing. There were no differences in the average percentage of censored volumes (ADNI: 6±11%; DIAN 7±10%) between Aβ+ vs. Aβ- in ADNI or between mutation carriers vs. non-carriers in DIAN (all p>0.05). Note that all above described image processing steps were conducted independently in DIAN and ADNI, hence no data was merged between the two cohorts during any stage of data processing or analysis.

Assessment of functional connectivity and system segregation (SyS)

Functional connectivity was estimated in an ROI based manner, using 400 ROIs from the Schaefer fMRI atlas (see Figure 1) which covers the neocortex (Schaefer *et al.*, 2017). The 400 ROIs are grouped within seven large-scale functional networks (Figure 1A) in line with previous parcellations (Yeo *et al.*, 2011). Prior to all analyses, the Schaefer fMRI atlas was masked with sample-specific grey matter masks (i.e. voxels with at least 30% probability of belonging to grey matter within the ADNI or BioFINDER sample), thresholded at a probability of 0.3. ROI-to-ROI FC was estimated for each subject based on fully preprocessed fMRI data. Specifically, we extracted the mean fMRI timeseries for each of the 400 ROIs by averaging the signal across voxels falling within an ROI per volume. Mean ROI timeseries were then cross-correlated using Pearson-Moment correlation, yielding a 400x400 FC matrix that was subsequently Fisher-z transformed, autocorrelations were set to zero and only positive connections were retained. System segregation was computed for each of the seven networks from a previously established network parcellation (Schaefer *et al.*, 2017) as the difference between mean within network FC and mean FC of the network nodes to the remaining six networks (i.e. between-network FC), as

$$SyS = \frac{\overline{z_w} - \overline{z_b}}{\overline{z_w}}$$

where $\overline{z_w}$ is the mean connectivity of all nodes within a given network and $\overline{z_b}$ is the mean connectivity of all nodes of a given network to nodes outside of that network(Chan *et al.*, 2014). Global SyS was computed as the mean segregation across all seven networks and used for subsequent analyses.

To ensure that our analyses were not driven by the selection of a particular graph-metric, we additionally computed the modularity coefficient Q (Newman, 2004), which is an alternative measure to quantify the segregation of brain networks, using the following equation:

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

Where A_{ij} represents the connectivity between nodes i and j, k_i and k_j are the sum of the connectivity weights attached to nodes i and j, m is the sum of all connectivity weights in the graph, c_i and c_j are the communities of the nodes and δ is the Kronecker delta function. SyS and Q were highly correlated in both cohorts (DIAN: r=0.9, R^2=0.81, p<0.001; ADNI: r=0.86, R^2=0.74, p<0.001), supporting the notion that both metrics assess the same underlying construct of brain network segregation.

Statistics:

For DIAN, baseline demographic scores were compared between mutation-carriers and non-carriers using t-tests for continuous and chi^2 tests for nominal variables. For the ADNI sample, demographics were compared between diagnostic groups using ANOVAs for continuous variables and Chi^2 for nominal variables.

In DIAN, we first tested whether higher EYO was associated with worse cognitive performance (i.e. global cognitive and memory composite), using linear mixed models controlling for age, gender, education (fixed effects), family affiliation and random intercept (random effects). For our major hypothesis, we assessed next whether higher SyS attenuated the association between advanced EYO and cognitive performance in the ADAD mutation carriers. To this end, we

employed linear mixed models to test the interaction between SyS and EYO on cognition (i.e. global cognitive and memory composite), again controlling for age, gender, education, mean motion (i.e. framewise displacement) during the resting-state fMRI scan (fixed effects), family affiliation and random intercept (random effects). For analyses in DIAN, we used a Bonferroni-corrected alpha threshold of 0.025 (i.e. α=0.05 adjusted for two tests, that is one test on global cognition, the other on memory performance).

In the ADNI tau-PET sample, we used tau-PET in Braak-stage I and III regions as markers of early core AD pathology. We preferred tau-PET over amyloid PET as a marker of disease progression, given tau-PETs' superior correlation with neurodegeneration and cognitive decline in AD (Brier *et al.*, 2016; La Joie *et al.*, 2020). We first tested whether a higher tau-PET SUVR (i.e. Braak I+III composite) was associated with worse cognition (i.e. ADAS13 for global cognition and ADNI-MEM for memory performance), using linear mixed models controlling for age, gender, education, mean motion (i.e. framewise displacement) during the resting-state fMRI scan (fixed effects), study center and random intercept (random effects). Next, we again tested our major hypothesis whether higher SyS attenuated the effect of Braak I+III tau-PET SUVR on ADAS13/ADNI-MEM (i.e. SyS x Braak I+III tau-PET interaction) using linear mixed models controlling for age, gender, education, mean motion (i.e. framewise displacement) during the resting-state fMRI scan (fixed effects), study center and random intercept (random effects). As in DIAN, we employed a Bonferroni-corrected alpha threshold of 0.025, adjusting for two tests. To ensure that the above described analyses were not driven by the selection of SyS as a graph metric, we repeated the analyses using the modularity coefficient Q (as implemented in the R toolbox phenoClust) as an alternative measure of network segregation. All statistical analyses were performed in R statistical software (version 3.6.1).

RESULTS

Baseline subject characteristics are displayed in table 1. When comparing SyS scores between AD groups and controls, there was no difference in SyS between mutation-carriers and the non-carrier group ($F=2.388$, $p=0.124$, Figure 2A) of the DIAN sample. In ADNI, however, we found decreased SyS in Aβ+ as compared to Aβ- participants ($F=8.904$, $p=0.003$, Cohen's $d=-0.478$, Figure 2B).

System segregation attenuates cognitive deficits in familial AD

As a proxy ADAD disease severity in the DIAN sample, we employed EYO, which is associated with performance on measures of both global cognition ($\beta=-0.657$, Cohen's $d=-1.834$, $p<0.001$) and memory ($\beta=-0.590$, Cohen's $d=-1.376$, $p<0.001$) as shown by linear mixed effects models controlling for age, gender, education (fixed effects) and family affiliation and random intercept (random effects). To test our major hypothesis, we determined the interaction effect between system segregation and EYO on either global cognition or memory, controlling for gender, education, mean motion during the resting-state fMRI scan (i.e. framewise displacement; fixed effects), family affiliation and random intercept (random effects). As hypothesized, we found a SyS segregation by EYO interaction on global cognition ($\beta=0.209$, $p=0.007$, Cohen's $d=0.57$, Figure 3A), such that ADAD mutation-carriers with higher SyS had better global cognitive performance at a given level of EYO compared to ADAD mutation-carriers with lower SyS. The interaction effect remained significant after accounting for multiple testing. Testing the same interaction effect for memory performance, however, yielded non-significant results ($\beta=0.026$, $p=0.799$, Cohen's $d=-0.055$, Figure 3B). Using the modularity coefficient Q instead of SyS yielded consistent interaction effects with EYO on global cognition ($\beta=0.209$, $p=0.004$, Cohen's $d=0.650$, Supp. Fig. 1A) but not memory performance ($\beta=0.033$, $p=0.727$, Supp. Fig. 1B). Together, the analyses in the DIAN cohort suggest that higher

segregation of brain networks is associated with attenuated global cognitive decreases in ADAD.

System segregation attenuates the association between tau pathology and cognitive deficits in sporadic AD

We aimed to assess whether beneficial effects of SyS on cognition are evident in the more common sporadic form of AD. To this end, we tested in 156 Aβ+ ADNI participants whether higher SyS was associated with attenuated effects of primary AD pathology on cognition. As a measure of primary AD pathology that is strongly linked to cognition, we used a composite tau-PET SUVR score, summarizing tau-PET levels within Braak-stage specific ROIs 1 & 3. The tau-PET composite of Braak-stage ROIs 1&3 was significantly higher in Aβ+ than in Aβ- ($F=51.69$, $p<0.001$, Cohen's $d=0.809$, ANCOVA controlled for age gender and education) and higher tau-PET composite scores were strongly associated with worse global cognition (i.e. ADAS13 total score, $\beta=0.26$, Cohen's $d=0.613$, $p<0.001$) and memory (i.e. ADNI-MEM, $\beta=-0.372$, Cohen's $d=-0.622$, $p<0.001$) in the Aβ+ group (linear mixed models controlling for age, gender, education [fixed effects], study center and random intercept [random effects]). Analogous to our analyses in DIAN, we then tested the interaction between SyS and the tau-PET composite on global cognition (i.e. ADAS13 total score) memory (i.e. ADNI-MEM), controlling for age, gender, education, diagnosis and mean framewise displacement [fixed effects]) as well as study center and random intercept [random effects]. We found significant SyS by tau-PET composite interactions on both global cognition ($\beta=-0.268$ $p<0.001$, Cohen's $d=-0.569$, Figure 3C) and memory performance ($\beta=0.220$, $p=0.004$, Cohen's $d=0.488$, Figure 3D). Both interaction effects remained significant after accounting for multiple testing. As shown in Figures 3C and D, higher SyS was associated with less severe global cognitive and memory impairment at a given level of tau pathology. Tau-PET was not associated with lower

SyS in ADNI Aβ+ subjects. Repeating the above described analyses with the modularity coefficient (i.e. tau-PET by modularity interaction), yielded consistent results for global cognition (β=-0.175, p=0.021, Cohen's d=-0.393, Supp. Fig. 1C) and memory (β=0.180, p=0.015, Cohen's d=0.413, Supp. Fig. 1D). The modularity index *Q* was not associated with tau PET ($p > 0.05$). When repeating the analyses in the Aβ- group, no significant tau-PET composite by SyS or tau-PET composite by modularity interaction effects were found (all $p>0.05$, see Supplementary Figure 2), suggesting that effects were specific for the Aβ+ group. These findings support the hypothesis that higher segregation of brain networks supports higher cognitive performance in the face of AD pathology.

Discussion

We found that higher resting-state fMRI-assessed SyS was associated with attenuated cognitive deficits in autosomal dominant AD and sporadic AD, such that higher SyS predicted a lower impact of disease progression markers (including EYO and tau PET) on cognitive performance. All findings were replicated with the modularity coefficient Q, i.e. an alternative graph metric for segregation between brain networks. Although our findings do not imply that the segregation of brain networks has a causative effect, these results strongly support a protective role of SyS on cognitive changes during the course of AD.

SyS was associated with altered effect of core AD progression markers on cognition, providing the first evidence that higher SyS is not only associated with higher cognition in normal aging shown previously (Chan *et al.*, 2014; Varangis *et al.*, 2019), but also with higher CR in AD. We found the same pattern of results when using the alternate index of modularity Q. Although computationally different, both indices are conceptually closely related by quantifying the extent to which functional connections segregate into densely connected networks (Wig, 2017). Thus, across different graph theoretical indices, we found that higher segregation of networks is associated with enhanced CR. We validated our findings across different cohorts including autosomal dominant AD and sporadic AD. ADAD provides a unique opportunity to study CR-related mechanisms in AD, where the confounding influence of age-related pathologies such as hypertensive cerebrovascular disease are unlikely due to early disease onset (Bateman *et al.*, 2011). However, although pathological brain alterations in ADAD are largely comparable to those in sporadic late-onset AD (Bateman *et al.*, 2011; Bateman *et al.*, 2012; Gordon *et al.*, 2018), there are important differences. Compared to sporadic AD, ADAD is associated with greater subcortical deposition of Aβ and higher occurrence of atypical “cotton wool” amyloid plaques (Day *et al.*, 2016). Therefore, the validation of our findings on the protective effects of SyS in sporadic AD is important. Together, these results provide evidence for a protective role of SyS in AD regardless of disease etiology.

In the current study, SyS was slightly reduced in participants with biomarker evidence of sporadic AD but not ADAD, however the overlap in SyS was large in ADNI between the AD and non-AD groups. One possible explanation for the inconsistency between ADNI and DIAN is that not all ADAD individuals yet showed elevated levels of AD pathology, which may have reduced our power to detect the small AD-related reduction in SyS. Our results of SyS decreases in sporadic, Aβ-positive participants are consistent with previous reports of reduced segregation of functional networks in elderly participants with elevated biomarker levels of Aβ (Brier *et al.*, 2014). The reduction of SyS in participants with elevated levels of Aβ raises the possibility that individuals with higher SyS had simply less severe AD pathology and thus lower cognitive impairment. However, we consider this explanation unlikely. Note that we tested the interaction effect of SyS by tau-PET on cognition, where in individuals with higher SyS, the decrease in cognition per unit increase in tau pathology was attenuated. Therefore, the critical test for CR was whether SyS was associated with an attenuated effect of tau PET on cognitive impairment rather than the level of tau pathology per se. Moreover, within the group of amyloid-PET positive participants, SyS was not related to amyloid PET levels or tau PET, where SyS was still associated with an attenuated association between tau PET and cognitive decline. Thus, the association between SyS and CR cannot be simply attributed to lower levels of core AD pathology in individuals with higher SyS.

The specific functional mechanisms that link SyS to higher cognitive performance are not fully understood. A recent theoretical framework suggested that SyS could be regulated by multiple control mechanisms such as hub connectivity in cognitive control networks (Medaglia *et al.*, 2017; Bertolero *et al.*, 2018). Higher system segregation is under the tight control of hubs, i.e. highly connected regions that are thought to be central to brain function (Ito *et al.*, 2017). In cognitively normal individuals, higher connectivity between hubs and major networks in the brain are associated with higher segregation of functional networks, which, in turn, are associated with higher cognitive performance across different cognitive domains (Bertolero *et*

al., 2018). We and others have previously shown that both higher resting-state and task-related functional connectivity of a global hub in the cognitive control network is associated with higher CR (Franzmeier *et al.*, 2017a; Franzmeier *et al.*, 2017b; Franzmeier *et al.*, 2017c; Franzmeier *et al.*, 2018a; Franzmeier *et al.*, 2018c; Neitzel *et al.*, 2019a). In addition, functional connectivity and activity of the anterior cingulate, another hub in the brain linked with higher modularity and higher general cognitive function (Hilger *et al.*, 2017; Tang *et al.*, 2019), has been repeatedly associated with higher CR in aging and AD (Arenaza-Urquijo *et al.*, 2013; Arenaza-Urquijo *et al.*, 2019). Together, these findings suggest that higher SyS may be a downstream final pathway of functional topology of the brain that supports CR in AD. Here, it is important to consider that our results are based on resting-state fMRI which may act as a baseline reference of functional brain organization from which task-specific network changes occur (Cole *et al.*, 2016; Wig, 2017). Brain network interactions have been shown to dynamically change during task-demands, depending on whether a given cognitive task requires information integration or segregation across networks (Cole *et al.*, 2013; Cohen and D'Esposito, 2016). Thus, it will be a critical next step to assess whether higher resting-state SyS is associated with task-specific network reorganization and cognitive performance. A further open question is whether the interindividual differences in SyS are persistent throughout life and which factors may have caused such differences. Note that we used the term cognitive resilience (CR) rather than cognitive reserve in the current study to remain agnostic to varies sources of influence that may have determined or shaped SyS. Life span studies are need to address genetic (Dumitrescu *et al.*, 2020), life style (Livingston *et al.*, 2020) and age-specific factors (Chan *et al.*, 2018a) that influence SyS.

Limitations

One limitation is that we assessed SyS based on a priori defined large-scale resting-state networks rather than networks/modules defined at the individual level. Network boundaries

may change during aging and disease, and thus the measure of SyS and modularity Q based on pre-defined networks may be altered due to ill-defined networks. However, large-scale resting state networks have been shown to be highly reproducible in aging and AD. A major advantage of choosing canonical resting state networks as the basic units is the increased interpretability of the findings, given the extensive cognitive characterization of such networks (Smith *et al.*, 2009). An alternate computation of the modularity index Q is based on a data-driven determination of networks (Newman, 2006), including the search for the optimal clustering of functional connections. However, the modularity optimization search is a non-deterministic polynomial hard problem (Brandes *et al.*, 2008), where the optimization depends on multiple parameters without any hard criteria of choosing the best model (Betzel and Bassett, 2017). Therefore, from a clinical point of view, it is more attractive to resort to *a priori* well-established and cognitively characterized functional networks as the basic units of network analysis.

Another caveat is how stable and reproducible SyS is across time. FMRI connectivity estimation can be biased by physiological noise (e.g. respiratory and cardiac signals) and motion artifacts which may limit reliable estimation of SyS or Q (Power *et al.*, 2014; Geerligs *et al.*, 2017). To correct for motion artifacts we combined motion correction, motion regression and motion scrubbing, referring to the censoring of high-motion volumes from fMRI data, which has been shown to minimize the influence of motion on connectivity estimation (Power *et al.*, 2014). In addition, we included subject-specific average motion estimates as covariates in 2nd level statistical models to additionally correct the assessment of SyS by tau-PET (ADNI) or SyS by EYO (DIAN) interaction models for motion during the fMRI scan. While the currently employed motion correction pipeline has been motivated by previous work (Power *et al.*, 2014), we would like to acknowledge that other motion correction approaches methods have been also proposed, including data interpolation, principal-component based denoising etc., and there is currently no “best” motion-correction pipeline (Caballero-Gaudes and Reynolds, 2017). For physiological noise (e.g. respiratory and cardiac signals), there were no

consistent measures available across the cohorts, hence we encourage future studies to validate our findings using fMRI data with concurrent physiological recordings. Regarding test-retest reliability of the currently used fMRI measures, there is a dearth of data for SyS. However, previous studies on the modularity index *Q* show moderate test-retest variability, which was superior to the reliability of first order interregional connectivity measures (Braun *et al.*, 2012), e.g. commonly used pair-wise ROI-to-ROI correlations. Importantly, the size of inter-individual differences in modularity exceed that of temporal fluctuations of modularity within an individual (Stevens *et al.*, 2012), supporting the view that fMRI assessed modularity may serve as a fingerprint of cognitive resilience in participants.

Conclusions

We demonstrated for the first time that individuals with higher SyS exhibited attenuated cognitive impairment at a given level of AD pathology. Higher modular organization of the brain may thus play an important role in maintaining relatively well cognitive abilities in the face of AD pathology. The resting-state fMRI-based assessment of SyS provides thus both mechanistic insight into functional brain differences that support CR as well as a promising approach to develop a marker to predict progression of cognitive decline in AD.

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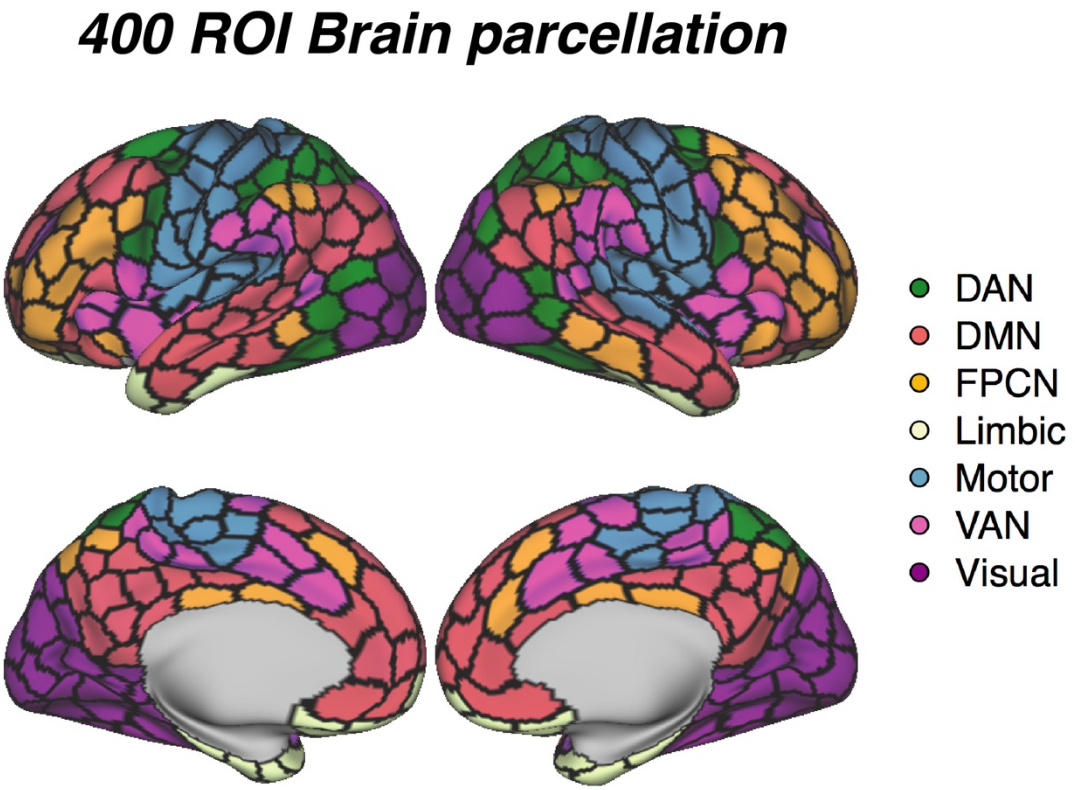
Table 1. Sample characteristics in each group

ADNI		CN Aβ- (n=184)	CN Aβ+ (n=89)	MCI Aβ+ (n=59)	AD Dementia (n=8)	p-value
	Age	72.3 (6.8)	75.8 (6.6)	76.3 (7.5)	73.5 (11.5)	<0.001
	Gender (f/m)	112/72	56/33	25/34	3/5	0.033
	Education	16.9 (2.3)	16.4 (2.5)	15.8 (2.7)	16.3 (2.3)	0.010
	ADAS13	12.2 (4.6)	13.6 (5.6)	22.8 (10.5)	31.7 (8.6)	<0.001
DIAN		Non-carrier (n=71)	Mutation-Carrier (n=108)			p-value
	Age	38.1 (10.3)	38.0 (10.5)			0.953
	EYO	-9.8 (11.0)	-8.6 (11.2)			0.470
	Gender (f/m)	44/27	68/40			0.990
	Education	15.2 (3.1)	14.2 (3.3)			0.033
	Global cognitive composite	0.19 (0.2)	-0.15 (0.5)			<0.001

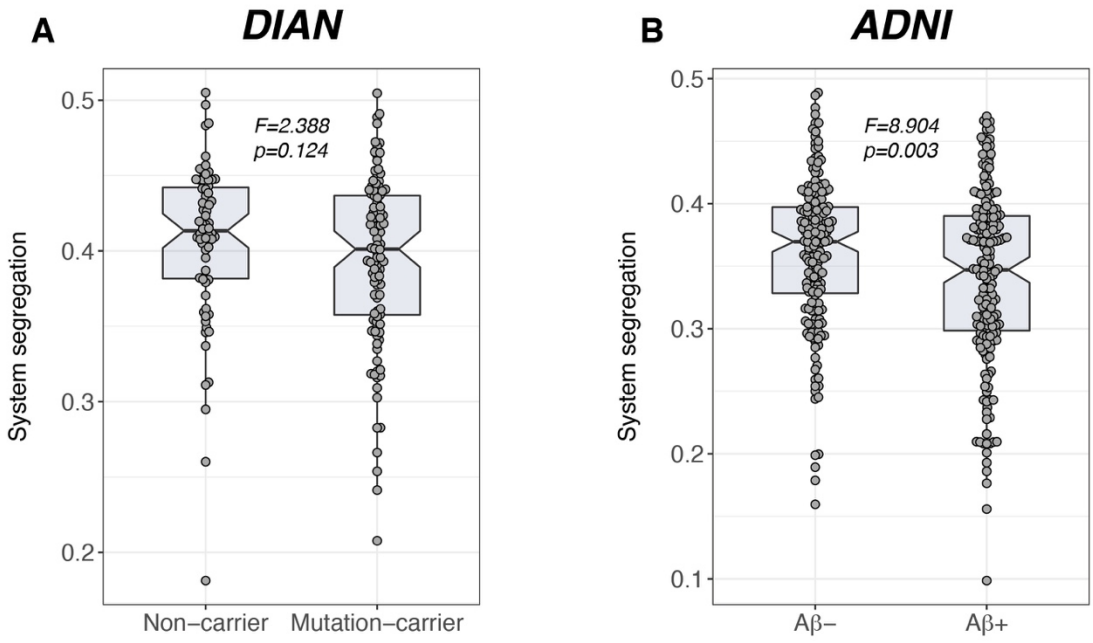
That classification of Aβ+ or Aβ-status was based on a previously established cut-point (global AV45 SUVR > 1.11) (Landau *et al.*, 2012). For continuous measures, the mean (and standard deviation) are displayed.

Figure 1:



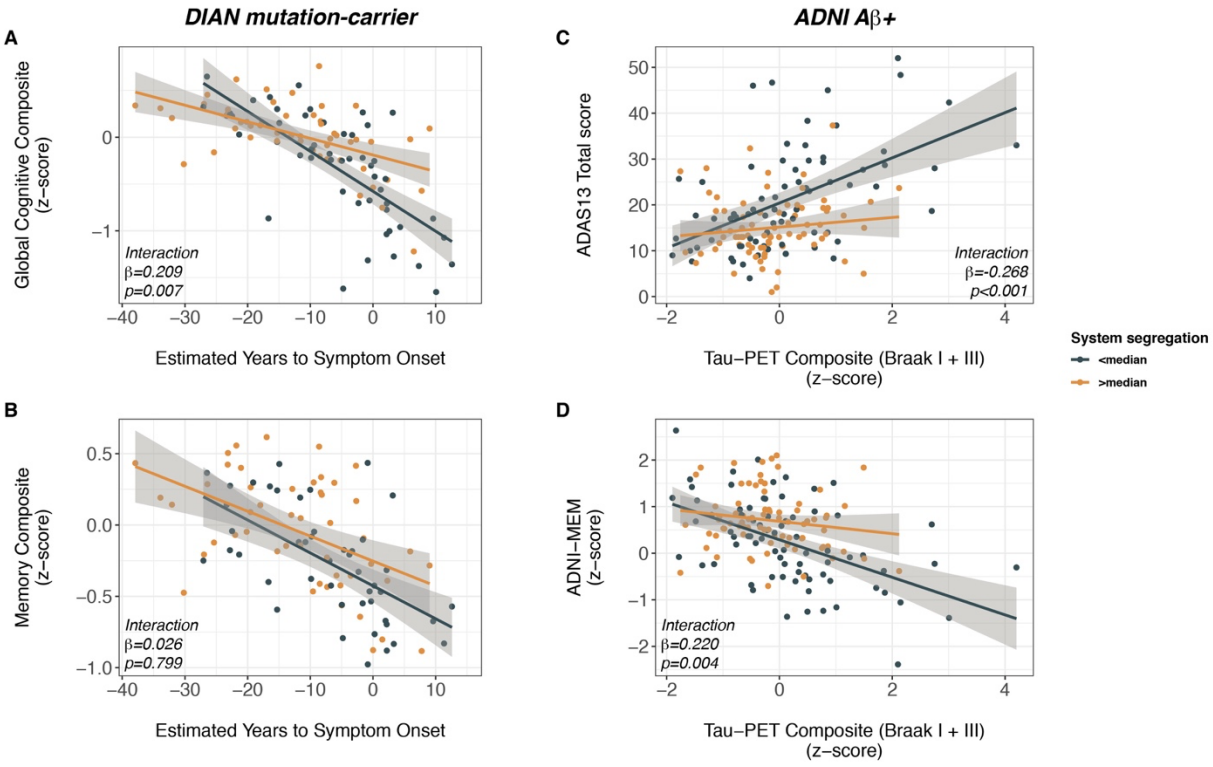
400-ROI Brain parcellation that was used to determine functional connectivity and system segregation between brain networks (Schaefer et al., 2017).

Figure 2:



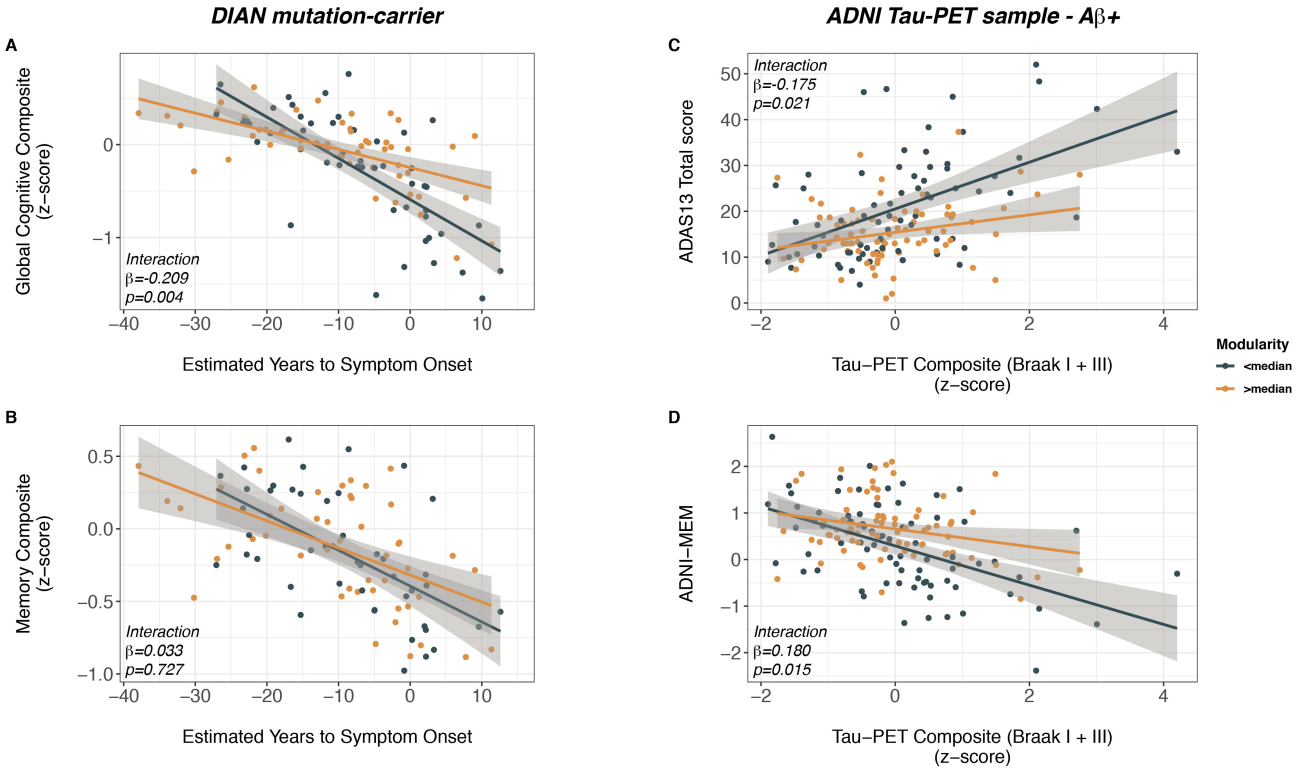
Group differences in system segregation between controls and patients with autosomal dominant (DIAN) and sporadic (ADNI) Alzheimer's disease.

Figure 3:



Interaction effect of system segregation by disease progression markers on cognitive performance in autosomal dominant (A and B) and sporadic Alzheimer's disease (C and D). Note that interaction effects were determined using continuous values of system segregation, while median splits are for illustrational purposes only. Note that higher scores on the ADAS13 (panel C) indicates worse cognition, whereas higher scores on the composite measures (A,B, and D) indicate better cognition.

Supplementary Figure 1:



Interaction effect of modularity Q by disease progression markers on cognitive performance in autosomal dominant (A&B) and sporadic Alzheimer's disease (C&D). Note that interaction effects were determined using continuous values of system segregation, while median splits are for illustrational purposes only. Note that higher scores on the ADAS13 (panel C) indicates worse cognition, whereas higher scores on the composite measures (A,B, and D) indicate better cognition.