Amyloid-associated hyperconnectivity drives tau spread across connected brain regions in Alzheimer's disease

Sebastian N. Roemer*,[1,2] Fabian Wagner*,[2] Lisa Evangelista,[2] Boris Rauchmann,[3,4] Amir Dehsarvi,[2] Anna Steward,[2] Anna Dewenter,[2] Davina Biel,[2] Zeyu Zhu,[2] Julia Pescoller,[2] Mattes Gross,[2] Robert Perneczky,[5,6,7,8,9] Maura Malpetti,[10] Michael Ewers,[2,6] Michael Schöll,[11,12,13] Martin Dichgans,[2,6,7] Günter U. Höglinger,[1,6,7] Matthias Brendel,[6,14] Sarah Jäkel,[2] Nicolai Franzmeier[2,6,11] for the Alzheimer's Disease Neuroimaging Initiative

*contributed equally

Affiliations

1. Department of Neurology, University Hospital, LMU Munich, Germany
2. Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany
3. Department of Neurology, University Hospital, LMU Munich, Germany
4. Department of Neuroradiology, University Hospital, LMU Munich, Germany
5. Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany
6. Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
7. German Center for Neurodegenerative Diseases (DZNE) Munich, Munich, Germany
8. Aging Epidemiology (AGE) Research Unit, School of Public Health, Imperial College London, London, UK
9. Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, UK
10. Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
11. University of Gothenburg, The Sahlgrenska Academy, Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Mölndal and Gothenburg, Sweden
12. Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden
13. Dementia Research Centre, Queen Square Institute of Neurology, University College London, UK
14. Department of Nuclear Medicine, University Hospital, LMU Munich, Germany

Correspondence to:
Dr. Nicolai Franzmeier
nicolai.franzmeier@med.uni-muenchen.de
Feodor-Lynen Str. 17
81377 Munich
Germany

Kommentiert [DN1]: Please add postal codes for all affiliations

Formatiert: Links

OVERLINE: NEURODEGENERATION

One sentence summary: Aβ induces neuronal hyperconnectivity, which promotes tau spreading from temporal lobe epicenters to connected brain regions in Alzheimer's disease

Editor's Summary

ABSTRACT

In Alzheimer's disease, Aβ triggers the aggregation and spreading of tau pathology which drives neurodegeneration and cognitive decline. However, the pathophysiological link between Aβ and tau remains unclear, which hinders therapeutic efforts to attenuate Aβ-related tau accumulation. Aβ has been found to trigger neuronal hyperactivity and hyperconnectivity, and preclinical research has shown that tau spreads across connected neurons in an activity-dependent manner. Therefore, Aβ may induce neuronal hyperactivity and hyperconnectivity thereby promoting tau spread across connected brain regions. By combining Aβ-PET, resting-state fMRI and longitudinal tau-PET in 69 cognitively normal controls devoid of amyloid pathology and 140 patients with a positive amyloid-PET scan covering the AD spectrum, we confirmed that Aβ induces hyperconnectivity of temporal lobe tau epicenters to posterior brain regions that are vulnerable to tau accumulation in AD. This was replicated in an independent sample of 55 controls and 345 individuals with preclinical AD and low cortical tau-PET uptake, suggesting that the emergence of Aβ-related hyperconnectivity precedes neocortical tau spreading typically observed in clinical stages of AD. Lastly, using longitudinal tau-PET, we confirmed that Aβ-related connectivity increases of tau epicenters to other brain regions mediated the effect of Aβ on faster tau accumulation. Together, these findings suggest that Aβ promotes tau spreading by eliciting neuronal hyperconnectivity and that targeting Aβ-related neuronal hyperconnectivity may attenuate tau spreading in AD.

hat verschoben (Einfügung) [1]

Kommentiert [DN2]: This needs to be no longer than 150 characters including spaces and is used as a teaser on the website

Kommentiert [DN3]: This will be provided by us.

Kommentiert [DN4]: Abstract should be no longer than 250 words, please check after edits.

hat gelöscht: Aβ-negative

Kommentiert [DN5]: As per our style, we prefer the form 'patients with AML' instead of 'AML patients' in order to avoid identification of the subjects with the disease.

hat gelöscht: Aβ-positive

hat gelöscht: across

hat gelöscht: Aβ-negative

hat gelöscht: Aβ-positive

hat gelöscht:

hat gelöscht: levels

hat gelöscht: Supporting the notion that fMRI-detected hyperconnectivity may mirror Aβ-associated neuronal hyperactivity, we found that compared to controls, neurons in a small AD post-mortem dataset expressed higher c-Fos, a Calcium-sensitive marker of ante-mortem neuronal activity.

hat gelöscht: via

hat gelöscht: hyperactivity and

hat nach oben verschoben [1]: ¶

INTRODUCTION

Alzheimer's disease (AD) is initiated by brain-wide amyloid-β (Aβ) accumulation, followed by the spread of neurofibrillary tau pathology from the temporal lobe across connected brain regions, ensuing neurodegeneration and cognitive decline.(*1-4*) This well-established amyloid-cascade model of AD is strongly supported by genetics and in vivo biomarker studies,(*5-7*) showing that mutations in Aβ-associated genes *APP, PSEN1* and *PSEN2*(*8*) but not in tau-associated genes such as *MAPT* (*9*) can cause full AD pathology in humans, including Aβ plaque and tau tangle formation. Furthermore, neuropathological and neuroimaging studies have demonstrated tau pathology to arise in the medial temporal lobe, in regions belonging to Braak stages I and II, in a large proportion of cognitively normal elderly as well as AD patients (*10-12*), whereas the dispersion of tau pathology to temporo-parietal brain regions of Braak stages III and IV is strongly dependent on concomitant Aβ pathology (*11, 12*). Thus, Aβ is assumed to trigger the spreading of tau from the medial temporal lobe to the neocortex, which constitutes the major driver of neurodegeneration and cognitive decline in AD(*13, 14*) and it is therefore of pivotal clinical interest to understand the link between Aβ and tau to therapeutically target the Aβ-tau axis.

Preclinical studies have shown that Aβ-oligomers can directly trigger tau phosphorylation in cultured hippocampal neurons(*15*) and that Aβ promotes the local aggregation of soluble tau in combined Aβ and tau transgenic mice.(*16*) However, post-mortem and PET studies in AD patients have consistently shown that Aβ and tau accumulation patterns are spatially distinct, especially in early stages of AD, with Aβ accumulating rather diffusely in the neocortex (*17-19*), whereas tau typically emerges rather focally in the medial temporal lobe with subsequent spread to connected neocortical regions.(*2, 20, 21*) Due to the spatial mismatch between Aβ and tau deposition patterns, it is unlikely that tau accumulation in AD is entirely induced by local Aβ. In addition, age-related medial temporal lobe tau pathology also occurs in the absence of cortical Aβ, suggesting that Aβ and tau accumulation can start independently of each other.(*22, 23*)

Our lead hypothesis that cortical Aβ indirectly triggers the spreading of tau pathology(*22, 23*) from local epicenters defined as regions with highest tau pathology at a given point in time, across connected brain regions by inducing neuronal hyperactivity and hyperconnectivity offers an alternative explanation for the link between Aβ and tau.(*24, 25*) This hypothesis is based on in vitro studies which have shown that tau is actively released from neurons and spreads across synaptic connections and that the rate of neuronal tau release and trans-synaptic spread is dependent on neuronal activity.(*24, 26, 27*) Congruently, PET-assessed tau pathology expands from local epicenters to regions that are functionally connected and show correlated neuronal activity on MEG

hat gelöscht: (i.e. *MAPT*)
hat formatiert: Schriftart: Kursiv
hat gelöscht: ,
hat gelöscht: i.e.
hat gelöscht: of
hat gelöscht: while
hat gelöscht: regions
hat gelöscht: i.e.
hat gelöscht: (i.e., precuneus, posterior cingulate, medial orbitofrontal cortex)
hat gelöscht: while
hat gelöscht: (i.e.
hat gelöscht:)

and resting-state fMRI.(*2, 28-35*) Aβ has previously been described as a potent trigger of neuronal hyperexcitability, increased neuronal firing and hypersynchronicity in cell and animal models,(*36-41*) explained by increased Glutamate release(*42*), reduced GABA sensitivity(*43*), and increased postsynaptic Ca^{2+}-influx.(*44*) Further, functional MRI (fMRI) studies have reported Aβ-related functional connectivity increases as measured by higher inter-regional synchrony of neuronal activity(*45*) in Aβ-transgenic mice and AD patients (*46-50*). In fact, changes in functional connectivity in AD patients are considered to occur early in AD when Aβ is the dominant pathology, where a cascading network failure is associated with the progression of AD pathophysiology (*50-54*). In addition, patients suffering from autosomal dominant and sporadic AD show an increased prevalence of subclinical epileptiform neuronal activity and seizures at early disease stages, together supporting the notion that Aβ induces an increase in neuronal activity and connectivity.(*55-59*)

We hypothesize that an Aβ-related increase in neuronal activity and connectivity is critical for triggering the trans-neuronal spread of tau, since enhanced neuronal activity amplifies synaptic tau release(*60*) and exacerbates trans-synaptic tau spread.(*24*) Supporting this, recent work in combined Aβ and tau transgenic mice has specifically shown that Aβ-associated neuronal hyperactivity triggers tau spread from the entorhinal cortex to connected regions.(*61*) However, it is not known whether Aβ-induced increases in neuronal activity and connectivity actively contribute to the spreading of tau pathology across interconnected brain regions in AD patients. Establishing this link bears a high potential to therapeutically attenuate tau spreading in AD and thus halt neurodegeneration and cognitive decline(*25*).

To address this, we included 209 participants from the Alzheimer's disease Neuroimaging Initiative (ADNI), encompassing 69 Aβ-negative (Aβ–) cognitively normal (CN) controls and 140 Aβ-positive (Aβ+) patients across the preclinical to dementia spectrum of AD, with available amyloid-PET and 3T resting-state fMRI to model functional connectivity and Aβ-related connectivity increases, as well as longitudinal [^{18}F]Flortaucipir tau-PET with approximately 2.7 years of follow-up to model the accumulation and spread of tau pathology. In this dataset, we tested i) whether regional Aβ deposition induces connectivity increases to epicenters of earliest tau deposition, ii) whether stronger connectivity of tau epicenters to a given brain region is linked to faster tau accumulation in that region and iii) whether accelerated spread of tau across connected regions is mediated by Aβ-associated connectivity increases. Cross-sectional analyses between Aβ and connectivity increases of tau epicenters were replicated using baseline amyloid-PET, tau-PET

hat gelöscht: (i.e.,
hat gelöscht:)
hat gelöscht: i.e.,
hat gelöscht: i.e.,
hat gelöscht: over
hat gelöscht: ~

and resting-state fMRI data of 345 preclinical AD patients (cognitively normal, Aβ+) and 55 Aβ-controls of the A4 study.

hat gelöscht: i.e.

hat gelöscht: Lastly, we aimed to support the notion of a potential role of Aβ in triggering neuronal hyperactivity in AD patients, by exploratorily assessing the proportion of c-Fos (i.e., an established marker of neuronal activity) expressing neurons in a small AD post-mortem brain tissue dataset compared to non-demented controls. (*62*)

RESULTS

Our primary neuroimaging sample from the ADNI database included 209 subjects, with 69 controls devoid of amyloid pathology (CN-Aβ-) and 140 Aβ+ subjects across the preclinical to dementia spectrum of AD (68 CN-Aβ+, 47 Mild Cognitive Impairment [MCI]-Aβ+, 25 Dementia-Aβ+). All ADNI subjects had available baseline Florbetaben (n=71) or Florbetapir (n=138) amyloid-PET, 3T resting-state fMRI and longitudinal Flortaucipir tau-PET with a mean follow-up time of 2.74 years. Clinical characteristics and patient demographics are shown in Table 1. Amyloid and tau-PET SUVRs were parcellated into 200 cortical ROIs using the Schaefer atlas, excluding typical subcortical sites of Flortaucipir off-target binding.(*62, 63*) For amyloid-PET data, regional and global amyloid-PET data were intensity normalized to the whole cerebellum and transformed to centiloid to harmonize Florbetaben and Florbetapir amyloid-PET tracers.(*64*) Longitudinal change rates in tau-PET SUVRs obtained using an the inferior cerebellar grey reference were computed for each ROI using a previously established approach, employing linear-mixed effects models controlling for random slope and intercept.(*29*) Surface renderings of baseline tau-PET SUVRs are shown Figure 1A, illustrating increasing tau-PET load across the AD spectrum. Longitudinal tau-PET change rates are shown in Figure 1B, showing overall faster tau-PET increase in AD spectrum patients vs. CN Aβ- subject. For validation of cross-sectional analyses regarding the association between Aβ and connectivity increases, we included data from 400 CN participants of the A4 study (55 CN-Aβ-, 345 CN-Aβ+), with available cross-sectional Florbetapir amyloid-PET, Flortaucipir tau-PET and 3T resting-state fMRI (see Table 1 for demographics).

Amyloid is associated with increased connectivity of tau epicenters to posterior brain regions

Our first aim was to determine whether regional Aβ is associated with functional connectivity increases of tau epicenters. To address this, we first determined subject-specific tau epicenters in Aβ+ subjects, defined as 5% of cortical brain regions with highest baseline tau-PET SUVRs (Fig. 2A), following our previously established protocols.(*2, 31, 65*) Subject-specific tau epicenters were subsequently used as seed regions for assessing subject-level resting-state functional connectivity to the remaining 95% non-epicenter brain regions (Fig. 2A-D). A group-average mapping of epicenter location and epicenter connectivity of the ADNI Aβ+ subjects is shown in Figure 2E, illustrating that tau epicenters are typically located in the inferior temporal lobe and show strong connectivity to posterior brain regions (Fig. 2F). We then assessed whether Aβ is linked to a strengthening of the connectivity between the tau

Kommentiert [DN21]: Please note: For experiments with n < 20, we ask that data be reported in tabular format. This is most easily accomplished with a separate Excel file with data from figures organized on separate tabs. Excel sheet should be uploaded as supplemental materials and labeled 'Data file S1' or something similar. Please see the Revision Checklist for additional instructions.

hat gelöscht: i.e.,

hat gelöscht: SUVRs

hat gelöscht: (i.e.

hat gelöscht:)

hat gelöscht: were

hat gelöscht: (i.e. intensity normalized to

hat gelöscht:)

hat gelöscht: (i.e. 10 ROIs)

epicenters and target regions. To this end, we determined ROI-wise linear regression models with functional connectivity between the tau epicenter and the target ROI as the dependent variable, and Aβ load defined as centiloid averaged across the tau epicenter and target ROI to account for Aβ at both ends of the connection as a predictor, controlling for age, sex, ethnicity, diagnosis, MRI scanner type and average motion during the resting-state fMRI scan as determined by mean framewise displacement. Supporting our hypothesis, we found that higher Aβ was associated with stronger connectivity of tau epicenters to widespread posterior temporo-parietal brain regions that typically accumulate tau relatively early in the course of AD ((*12, 21, 66*) Fig.3A). To illustrate this point further, the average centiloid values vs. tau epicenter connectivity of significant regions described in Fig. 3A is shown in Fig. 3B, confirming that higher Aβ is related to stronger connectivity. In addition, we determined the overall distribution of the regression derived beta-values of the association between centiloid and connectivity (Fig. 3C), showing that beta-values were significantly greater than zero (95%CI=[0.10;0.14], T=11.693, p<0.001). This result pattern supports our hypothesis that Aβ is linked to an overall connectivity increase of the tau epicenter to the rest of the brain. Supporting the robustness of these findings, these results were replicated in 345 Aβ+ subjects with preclinical AD of the A4 sample, showing a highly congruent spatial pattern of Aβ-related connectivity increases of tau epicenters to posterior brain regions (Fig. 3D). This result was also congruent when reclassifying Aβ-positivity in A4 subjects at a slightly more restrictive amyloid-PET SUVR threshold of 1.15 as previously suggested by the A4 imaging core (see Fig.S1).(*67*) Similar results were obtained when restricting the ADNI cohort to cognitively normal Aβ+ subjects (n=68) to match the A4 cohort of preclinical AD subjects (Fig.S2), overall supporting the view that Aβ-related connectivity changes occur early in AD. All results were specific for Aβ+ subjects, as no associations between Aβ and tau epicenter connectivity were detected in Aβ- subjects of ADNI or A4.

To investigate further if Aβ-related connectivity increases were specific to tau epicenters, we examined the correlation of the connectivity between two ROIs and their average amyloid-PET centiloids for each Aβ+ subject. We created a 200x200 amyloid load matrix for each subject, representing cumulative amyloid levels across ROI pairs, which we then correlated with the subject-specific functional connectivity matrix. The results showed positive correlations between amyloid load and connectivity across ROI pairs within Aβ+ subjects of ADNI (T=4.571, p<0.001) and A4 (T=7.793, p<0.001), indicating that ROI pairs with higher amyloid loads tend to have higher connectivity, regardless of being a tau epicenter or not (see Fig.S3).

hat gelöscht: (i.e.

hat gelöscht:)

hat gelöscht: (i.e.

hat gelöscht:)

hat gelöscht: , i.e., brain regions

hat gelöscht: level

hat gelöscht: (i.e. centiloid)

hat gelöscht: i.e.

hat gelöscht: highly

hat gelöscht: significant

hat gelöscht: levels

hat gelöscht: level

Using an alternative metric of neuronal activity (FDG-PET to measure cortical glucose consumption intensity normalized to the Pons) that was available in a subset of Aβ+ ADNI patients (n=61) confirmed that higher regional amyloid-PET was related to higher glucose metabolism (mean/SD subject-level correlation between regional amyloid-PET and FDG-PET=0.33/0.16; 95%CI=[0.29,0.38], T=15.91, p<0.001). Together, these results suggest that Aβ is linked to increased functional connectivity potentially driven by neuronal hyperactivity.

Regions that are more strongly connected to the tau epicenter show faster tau accumulation

Next, we addressed our second aim whether stronger connectivity of the tau epicenter to other brain regions is associated with faster tau accumulation in those regions, indicative of faster tau spread across connections. This analysis was performed using ADNI data only, as no longitudinal tau-PET data were available in A4. We performed ROI-wise regression models in Aβ+ subjects, assessing whether higher subject-specific connectivity of the tau epicenter to a given region predicted faster tau-PET change rates in that region, controlling for age, sex, ethnicity, diagnosis, MRI scanner type and motion during the fMRI scan. We found widespread associations (p<0.05, FDR-corrected) between tau epicenter connectivity and faster tau accumulation, predominantly for temporo-parietal, occipital and superior frontal brain regions (see Fig. 4A) showing wide overlap with regions in which we detected Aβ-related connectivity increases (see black outline in Fig.4A). When assessing the distribution of region-specific associations between epicenter connectivity and tau-PET increase over time (regression derived beta-values displayed in Fig. 4A), beta values were greater than zero (95%CI=[0.16;0.2], T=20.012, p<0.001, Fig. 4B), suggesting that higher epicenter connectivity is overall related to faster tau accumulation. Importantly these results were obtained using subject-level connectivity data, showing that patient-specific connectivity patterns and strength are relevant for tau spreading. Together, these results support the hypothesis that brain regions that are more strongly connected to the tau epicenters on the individual level show faster tau accumulation over time, in line with the concept of trans-neuronal tau spreading.

The association between Aβ and tau accumulation is mediated by Aβ-related connectivity increases

For our third aim, we assessed Aβ-induced connectivity changes as a putative pathophysiological link between Aβ and tau spreading. Again, this analysis was restricted to

hat gelöscht: i.e.

hat gelöscht: ¶ ... [1]

hat gelöscht: , i.e.

hat gelöscht: level

hat gelöscht: significant

hat gelöscht: 5A

hat gelöscht: 5A

hat gelöscht: i.e.

hat gelöscht: significantly

hat gelöscht: i.e.

hat gelöscht: 5B

the ADNI dataset with available longitudinal tau-PET. In the ADNI Aβ+ subjects, we determined ROI-wise bootstrapped mediation models with 1000 iterations, testing whether higher Aβ (centiloids averaged across the tau epicenter and any given target ROI) was linked to faster tau accumulation in a given target ROI, and whether this effect was mediated by a Aβ-related functional connectivity increases between the target ROI and the tau epicenter (concept illustrated in Fig.4C). All mediation models were controlled for age, sex, ethnicity, diagnosis, MRI scanner type and motion during the fMRI scan and FDR-corrected for multiple comparisons ($p<0.05$). Supporting our hypothesis, we found that faster tau-PET accumulation in temporo-parietal regions were mediated by Aβ-related connectivity increases of these brain regions to the tau epicenter (Fig. 4C and D). Taken together, these results favor a pathophysiological disease model in which regional Aβ induces stronger functional connectivity to the tau epicenter, which in turn facilitates the spreading of tau from the epicenters to connected brain regions.

hat gelöscht: i.e.

hat gelöscht: 5C

hat gelöscht: 5C

DISCUSSION

Aβ deposition has been shown to trigger neuronal hyperactivity, hypersynchronicity and hyperconnectivity in animal and cell models(*39-41, 68*) and to be associated with epileptiform brain activity in AD mouse models and AD patients.(*37, 56-58*) We hypothesized that Aβ-induced neuronal hyperactivity manifests in functional connectivity increases (*52-54, 69*) and thereby accelerates the activity-dependent spread of tau pathology across connected brain regions in AD patients.(*24, 70*) Prior studies have identified functional connectivity increases in AD patients as one of the earliest pathological findings in AD, which has led to the formation of the cascading network hypothesis (*52-54*), which claims a key role of early network dysfunction in promoting AD pathophysiology. In the current study we aimed to integrate the insights on early changes of functional connectivity in AD with our previous findings on connectivity-based tau spreading to test whether Aβ-induced hyperconnectivity promotes tau spreading throughout connected brain regions.

Supporting this model, our first finding was that higher regional Aβ was linked to stronger resting-state fMRI-assessed functional connectivity of posterior temporal, parietal and occipital brain regions to temporal-lobe tau epicenters in 140 patients across the preclinical to clinical AD spectrum. Importantly, this result could be replicated in an independent sample of 345 patients with preclinical AD, suggesting that Aβ-related connectivity increases are an early event in AD that precedes brain-wide tau deposition. Second, we could confirm that stronger patient-level functional connectivity of tau epicenters to tempo-parietal, frontal and occipital brain regions was associated with faster tau accumulation in these regions, indicative of faster connectivity-mediated tau spread.(*2, 28, 29, 71*) Thirdly, we tested an integrative pathophysiological disease progression model, showing that the association between temporo-parietal Aβ deposition and faster tau accumulation in these regions is mediated by Aβ-driven connectivity increases to the tau epicenter. Together, our results suggest that Aβ induces neuronal hyperactivity and functional connectivity increases, in line with previous evidence from the cascading network failure model, showing Aβ-associated connectivity increases as a key feature of AD pathophysiology.(*53*) Most importantly, we could show that Aβ-associated connectivity increases facilitate the spreading of tau from epicenters to connected regions in AD. This finding embeds Aβ-associated connectivity increases as a key link between Aβ-deposition and tau spreading, thereby rendering Aβ-induced changes in neuronal activity and connectivity as a potential therapeutic target to attenuate tau spreading and subsequent neurodegeneration and cognitive decline in AD.

Kommentiert [DN48]: Please make sure to include a paragraph discussing the limitations of your study

hat gelöscht: Further supporting a role of Aβ in triggering neuronal hyperactivity, we included a small number of post-mortem samples from AD patients and controls, showing a higher proportion of c-Fos+ neurons in AD vs. controls in the visual cortex that typically shows high Aβ but low tau, indicative of elevated ante-mortem neuronal activity.(*71*)

Our first main finding in patients across the AD spectrum showed that regional Aβ deposition is associated with increased functional connectivity of temporo-parietal and occipital regions to tau epicenters typically located in the temporal lobe. This result pattern was replicated in an independent cohort of preclinical AD patients, in which neocortical tau deposition is typically low,(*72*) supporting a sequence of events in which Aβ-related connectivity increases precede and potentially accelerate the spread of tau across the neocortex.(*25*) Similarly, previous resting-state fMRI studies in Aβ-transgenic mice and preclinical AD patients reported Aβ-related functional connectivity increases within and between large scale brain networks,(*41, 45, 46, 73*), as also suggested by the cascading network failure model of AD (*52, 53*). More recently, a task-fMRI study in a small cohort of cognitively normal older individuals could further show Aβ-associated hyperconnectivity between the Default Mode Network and the medial temporal lobe during cognitive demands, suggesting that Aβ-related network changes interfere with neuronal processing very early in the disease process (*50*). Together, these findings provide converging evidence that Aβ can induce early-stage functional connectivity increases.

Consistent across both neuroimaging samples, the Aβ-associated connectivity increases were found primarily between temporal lobe tau epicenters and posterior brain regions which are also physiologically strongly connected to temporal lobe sites of earliest tau deposition.(*2*) Nevertheless, we also found small but brain-wide associations between Aβ-deposition and higher connectivity, as well as an association between higher Aβ and higher FDG-PET in a smaller subset of AD patients, supporting the view that Aβ is associated with hyperconnectivity and neuronal hyperactivity. Congruently, data from rodent models show that Aβ induces existing synapses to become hyperactive, rather than triggering synaptogenesis,(*40, 74*) together suggesting that Aβ leads to an upregulation and strengthened co-activation of pre-existing connections rather than the formation of new connections. From a mechanistic point of view, electrophysiological studies in Aβ-transgenic mice and AD patients have shown that Aβ-related hyperactivity and therefore connectivity is explained by a loss of inhibition and an excitatory shift in neuronal activity,(*75-77*) potentially due to Aβ-related alterations in Calcium clearance, as well as altered neurotransmitter release/sensitivity and synaptic vesicle release.(*42, 43, 75*) Since the BOLD signal that is used to determine functional connectivity has been shown to increase as a function of Calcium-dependent neuronal excitation,(*78*) the

hat gelöscht: (i.e. typically located in the temporal lobe)

hat gelöscht: -levels

hat gelöscht: Along the same lines, our exploratory post-mortem data analysis, despite a limited sample size, indicated that AD patients show an increased proportion of c-Fos positive neurons than controls. C-Fos expression is upregulated in response to Calcium influx and typically higher in hyperactive neurons,(*75, 76*) hence the elevated number of c-Fos positive neurons in the AD brain tissue samples potentially reflect elevated ante-mortem neuronal activity. This finding is in line with previous studies, showing that elevated c-Fos expression in AD patients in the medial temporal lobe, where tau typically emerges in very early AD stages.(*77, 78*) Importantly, we detected c-Fos positive neurons in the primary visual cortex, i.e. a brain region that typically has high Aβ but is typically less affected by tau pathology and tau associated neurodegeneration.(*20*) Supporting this, we did not find differing neuron counts between AD patients and controls in the examined samples, suggesting limited or absent tau-related neurodegeneration. Therefore, bearing in mind the relatively small sample size, our results suggest that the increased c-Fos signal relates to Aβ-associated processes, in line with animal data showing hyperactive neurons in the vicinity of Aβ plaques, yet these results require further confirmation in larger post-mortem cohorts.(*40*)

Aβ-related connectivity increases observed in our study may indeed reflect an excitatory shift in neuronal activity ensuing stronger inter-regional synchronicity and connectivity. However, the exact relationships between neuronal activity, Aβ and connectivity between brain regions remain unclear until specifically tested by combining markers of connectivity, electrophysiological activity, and biomarkers of Aβ. Nevertheless, our hypothesis-driven and translational findings provide robust evidence for Aβ to induce increased connectivity of the tau epicenter to connected brain regions.

For our second main finding, we could show that stronger patient-specific connectivity of large parts of the temporo-parietal, occipital and frontal cortex to tau epicenters is linked to faster tau accumulation in these brain regions. This finding strongly supports the concept of trans-neuronal tau spreading(*79, 80*) and robustly recapitulates our previous results, showing that the seed-based connectivity pattern of tau epicenters closely aligns with the spatial pattern of tau accumulation in AD patients.(*2, 3, 30*) Yet, a key novelty of our study is the combination of longitudinal tau-PET with subject-specific resting-state fMRI connectomics, compared to the previous usage of group average connectivity templates derived from healthy controls.(*2, 3, 30*) More specifically, our findings suggest that Aβ-associated changes of the patient-specific connectome influence the rate of tau spreading in AD.(*81*) This is closely in line with the results of a previous study in cognitively normal older adults, showing that Aβ-associated hyperconnectivity between the default mode network and the medial temporal lobe during cognitive demands is predictive of faster medial temporal lobe tau accumulation in these early tau vulnerable brain regions (*50*). Thus, the inter-individual heterogeneity in tau spreading patterns observed in AD and its clinical variants(*2, 34, 82*) is potentially not only determined by spatial heterogeneous locations of tau epicenters,(*2, 29, 82*) but also by inter-individual differences in the strength of functional connectivity and in particular by Aβ-induced connectivity changes.(*25, 50, 83*) Therefore, factors that have been related to altered functional brain network architecture and connectivity strength such as vascular health or neuroinflammation (*84, 85*) may also alter tau trajectories in AD.

Our third finding was that the influence of Aβ on faster tau accumulation is mediated by an Aβ-related functional connectivity increase of the tau epicenter to other brain regions. Importantly, this mediation effect was detected for typical tau vulnerable regions in the temporo-parietal cortex,(*20, 21*) suggesting that the spreading of tau pathology from epicenters to regions predominantly belonging to Braak stage regions III/IV is specifically facilitated by Aβ-related connectivity increases. From a biological point of view, Aβ-related neuronal

hat gelöscht: level

hat gelöscht: level

hat gelöscht: (e.g.,

hat gelöscht: ,

hat gelöscht:)

hyperactivity may trigger a stronger activity-dependent secretion of seeding-competent tau species from tau harboring neurons (*24, 79*) thereby increasing the likelihood that secreted and misfolded tau seeds taken up by a synaptically connected neuron where they induce template-based tau misfolding and aggregation. Supporting this, we have previously reported that elevated p-tau species that are newly synthesized and actively secreted into the CSF(*86*) drive the spreading of tau across connected brain regions.(*30*) This interpretation is also supported by previous studies in tau transgenic mice and cell models, showing that i) tau spreads specifically across synaptic connections and that ii) higher neuronal activity (triggered by opto-genetic stimulation of neuronal activity) induces faster neuronal tau secretion and trans-synaptic tau spreading.(*24, 79*) Overall, these results support a disease model, in which Aβ-related changes in neuronal activity and connectivity may play a key role in initiating the Aβ-related spread of tau across connected brain regions. Previous work has further suggested that the initial and relatively slow spreading of tau from the medial temporal lobe to the temporal cortex may be triggered by remote effects of Aβ in regions connected to initial medial temporal lobe tau epicenters ("pull-effect"), whereas the local convergence of Aβ and tau in the inferior temporal lobe leads to an acceleration of tau spread from the Aβ-tau convergence zones to connected brain regions ("push-effect").(*69*) It is possible that remote Aβ in regions not harboring any tau pathology triggers hyperactivity and hyperconnectivity to tau epicenters (*50*), thereby initiating the spread of local tau seeds from the medial temporal lobe to Aβ-harboring connected brain regions. Second, the regional convergence of Aβ and pathological tau seeds may foster local interactions between both pathologies, promoting stronger tau hyperphosphorylation and the generation of tau seeds, which may then lead to an acceleration of tau spreading (*87*). Therefore, disentangling potential remote and local interactions between Aβ and tau in the context of connectivity-associated tau spread and neuronal hyperactivity/connectivity will be an important field for future investigation, to better characterize the acceleration phase of Aβ-dependent tau accumulation and spread.

When interpreting the results of our study, several limitations should be considered. First, we used resting-state fMRI, which is based on the BOLD signal, and therefore an indirect proxy measure of neuronal activity. Connectivity is based on the quantification of co-fluctuations of the BOLD signal, hence our neuroimaging results do not directly provide evidence for Aβ-associated neuronal hyperactivity in AD patients but rather emphasize an increase of synchronicity between two regions harboring Aβ. However, since preclinical studies have

hat gelöscht: (e.g. via entering synaptic vesicles)

hat gelöscht: i.e.

hat gelöscht: i.e.

hat gelöscht: while

hat gelöscht: i.e.

hat formatiert: Schriftart: Symbol

hat gelöscht: , i.e.,

hat gelöscht: resulting

shown concomitant Aβ-associated neuronal hyperactivity and hyper-synchronicity which is equivalent to the definition of functional connectivity, we deemed resting-state fMRI an adequate measure to assess these changes by proxy.(*40*) In addition, we preformed exploratory sub-analyses in the ADNI cohort, showing that higher amyloid-PET are associated with higher regional glucose consumption in a subsample of Aβ+ subjects with available FDG-PET data (n=61), suggesting that higher amyloid pathology is indeed linked to higher neuronal activity. In addition, it will be a key next step to combine our current analysis framework with electrophysiological measures of neuronal activity such as EEG or MEG that allow a more direct quantification of the neuronal excitatory/inhibitory balance, as well as additional markers of neuronal activity or synaptic density. In addition, we employed resting-state fMRI to determine the existence of a connection between any set of brain regions, whereas it remains unclear whether a "functional" connection is enabled by a direct underlying "structural" axonal connection along which tau spreads.(*81, 88*) Rather, a functional connection may reflect both direct and indirect "multi-synaptic" connections.(*89*) Addressing this limitation by including individual structural connectomes would have required high-quality diffusion MRI to determine subject-level structural connectivity which would have drastically limited the sample size. Thus, we refrained from additionally including structural connectivity to constrain functional connections in the current study. Lastly, the cross validation in the A4 sample was restricted to cross-sectional analyses on Aβ vs. connectivity changes, since longitudinal tau-PET data are not yet available in this dataset. Therefore, the longitudinal associations between Aβ-related connectivity changes and faster tau spreading remain to be independently replicated once these data become available. Beyond the limitations, our study features several clear strengths, as we employed a fully hypothesis-driven approach to determine the role of connectivity changes in cross-linking Aβ accumulation and tau spreading. In addition, the study design included an independent replication sample illustrated the robustness of the association between Aβ and connectivity increases.

In conclusion, our findings provide evidence that Aβ-associated neuronal activity and connectivity changes may be a key missing link between the accumulation of Aβ and the subsequent spreading of tau pathology in AD. These findings are of high clinical importance, since modulating neuronal activity may be a promising target for attenuating Aβ-related tau accumulation and spreading. Previous trials repurposing anti-epileptic drugs to lower neuronal hyperexcitability and hyperactivity in AD patients have been tested, yet over relatively short

hat gelöscht: (i.e.

hat gelöscht:)

hat gelöscht: levels

hat gelöscht: FDG-PET

hat gelöscht: levels

hat gelöscht: levels

hat gelöscht: are

hat gelöscht: Further, we substantiated this hypothesis by the independent analyses on post-mortem tissue derived from a small AD patient and control group, showing an elevated proportion of c-Fos positive neurons in AD brains compared to controls, congruent with higher ante-mortem neuronal activity in AD patients. While the post-mortem data show an increase in the proportion of c-Fos positive neurons in AD vs. controls, we did not test a linear relationship between Aβ-load and c-Fos increases, due to the relatively restricted sample size and the exploratory nature of this analysis. However, the primary visual cortex usually harbors high Aβ and little tau tangle pathology and tau-related neurodegeneration in AD, which was supported by the non-significant differences in neuron count between AD patients and controls in a subset of these patients. Thus, it is likely that the c-Fos increase observed in the post-mortem data is related to Aβ deposition or an Aβ-associated process. However, given this small sample size, we would like to highlight that the post-mortem analyses should be considered rather exploratory and additive for the major neuroimaging findings and warrant further investigation using larger sample sizes that cover a broader spectrum of AD pathophysiology.

hat gelöscht: (e.g.

hat gelöscht: /

hat gelöscht:)

hat gelöscht: (e.g. SV2A-PET)

hat gelöscht: while

hat gelöscht: ¶ ... [2]

hat gelöscht: . First,

hat gelöscht: The

hat gelöscht: including

hat gelöscht: In addition, we implemented a translational study design, including exploratory post-mortem analyses which further substantiated the notion that Aβ is related to neuronal hyperactivity using ´issue samples from AD patient brains. …

timespans of several weeks, focusing on clinical endpoints (*56, 58, 90*). However, we reason that surrogate biomarker endpoints should be considered, such as the activity-dependent secretion of phosphorylated tau species detectable in CSF or plasma (*86*), or the long-term spreading and accumulation of tau pathology, which would require longer intervention periods in subjects at the early phase of Aβ-induced tauopathy. Such a treatment approach may be particularly promising in early-stage AD patients in addition to targeting Aβ, to target fibrillar Aβ deposition directly, as well as its consequences on tau spreading, to therefore maximize the likelihood to attenuate tau-related neurodegeneration and cognitive decline.(*13, 14, 91*) Together, our results should encourage others to further investigate neuronal activity and connectivity as key links between Aβ and tau, to help specifically target the Aβ-tau axis in AD.

Material and METHODS

Study design

The overall objective of this observational study was to determine whether amyloid deposition induces neuronal hyperconnectivity and hyperactivity, thereby driving tau spreading across interconnected brain regions. To this end, we used observational neuroimaging and biomarker data from the ADNI and A4 study for independent replication. No treatments or interventions were administered for the included individuals and data and no randomization was performed. We included the largest possible sample size that matched the inclusion criteria specified below, hence no a priori study sized calculations were performed. The authors were not blinded to the diagnosis or biomarker status of the included individuals.

hat gelöscht: Study Design¶

ADNI Participants

209 Subjects were included from the Alzheimer's disease Neuroimaging Initiative (ADNI) database, based on availability of clinical data, baseline 18F-Florbetapir/Florbetaben amyloid-PET, 3T resting-state fMRI and longitudinal 18F-Flortaucipir tau-PET data. All baseline data had to be obtained within a timeframe of 6 months. Participants diagnostic status was determined by ADNI as cognitively normal (CN; Mini Mental State Examination [MMSE]≥24, Clinical Dementia Rating [CDR]=0, non-depressed), mildly cognitively impaired (MCI; MMSE≥24, CDR=0.5, objective memory-impairment on education-adjusted Wechsler Memory Scale II, preserved activities of daily living) and demented (MMSE=20–26, CDR>0.5, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD). Amyloid status was determined on global amyloid-PET SUVRs using tracer-specific cut-offs at 1.11/1.08 for Florbetapir/Florbetaben, as previously established in the ADNI cohort.(*92, 93*) All study procedures were conducted in accordance with the declaration of Helsinki, ethical approval was obtained by ADNI investigators. All study participants provided written informed consent.

hat gelöscht: (i.e. SUVR

hat gelöscht:)

Feldfunktion geändert

A4 participants

For replication of cross-sectional analyses, we included baseline data from 400 participants of the A4 study, based on availability of clinical data, 18F-Florbetapir amyloid-PET, resting-state fMRI and [18F-Flortaucipir tau-PET obtained at the baseline study visit. All subjects were classified as CN (MMSE>25, CDR=0, Wechsler Logical Memory score of 6 to 18), as defined

hat gelöscht: subjects from the A4 trial

by the inclusion criteria of the A4 trial (https://clinicaltrials.gov/study/NCT02008357). Amyloid status was determined using global amyloid-PET SUVRs and the 1.11 global SUVR cut-off defined in the ADNI cohort. All study procedures were conducted in accordance with the declaration of Helsinki, ethical approval was obtained by A4 investigators. All study participants provided written informed consent.

Neuroimaging acquisition

Structural and functional MRI were acquired using 3T Siemens, GE and Philips scanners. T1-weighted structural scans were collected using an MPRAGE sequence (TR=2300ms; Voxel size=1x1x1mm; for parameter details see: https://adni.loni.usc.edu/wp-content/uploads/2017/07/ADNI3-MRI-protocols.pdf). Resting-state-fMRI was obtained using a 3D echo-planar imaging (EPI) sequence with 200 fMRI volumes per subject (TR/TE=3000/30ms; flip angle=90°; Voxel size=3.4x3.4x3.4mm).

PET data was assessed post intravenous injection of ^{18}F-labeled tracers (Flortaucipir: 6x5min time-frames, 75-105min post-injection; Florbetapir: 4x5min time-frames, 50-70min post-injection; Florbetaben: 4x5min time-frames, 90-110min post-injection; for more information see http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/). In a subset of ADNI participants, we also included FDG-PET data, recorded 6x5min frames 30-60min post-injection. A4 and ADNI imaging data were recorded using congruent imaging protocols.

Image processing

All images were screened for artifacts before preprocessing, and processing was conducted independently for the ADNI and A4 sample. T1-weighted structural MRI scans were bias-corrected, segmented, and non-linearly warped to Montreal Neurological Institute (MNI) space using the CAT12 toolbox (https://neuro-jena.github.io/cat12-help/). Dynamically acquired PET images were realigned and averaged to obtain single Flortaucipir/Florbetapir images which were rigidly registered to the T1-weighted MRI scan. As reference regions, we used the inferior cerebellar grey for Flortaucipir, the whole cerebellum for Florbetapir/Florbetaben, and the Pons for FDG-PET (*94, 95*) Reference regions and the cortical Schaefer atlas including 200 regions of interest (ROIs) were warped from MNI to T1-native space using the CAT12-derived non-linear normalization parameters, masked with subject-specific grey matter and applied to PET data to determine standardized uptake value ratios (SUVRs) for each region of the Schaefer 200 atlas.(*62*) Global and regional Florbetapir/Florbetaben SUVRs were converted to centiloid using equations provided by ADNI. To determine longitudinal tau-PET change, we

Feldfunktion geändert

Feldfunktion geändert

Feldfunktion geändert

hat gelöscht: each sample (i.e. ADNI vs. A4)

hat gelöscht: R

hat gelöscht: (i.e.,

hat gelöscht:)

Feldfunktion geändert

Feldfunktion geändert

employed linear mixed models controlling for random slope and intercept as described previously.(*2, 3*)

Resting-state fMRI images were slice-time corrected and realigned to the first volume for motion correction, followed by co-registration to the respective T1-weighted images. Using rigid-transformation parameters, T1-derived grey-matter, eroded white matter and eroded cerebrospinal fluid (CSF) segments were transformed to EPI space. To denoise EPI images, we regressed out nuisance covariates, including the timeseries of the eroded white matter and eroded CSF plus six motion parameters as well as their time and dispersion derivatives, followed by detrending and band-pass filtering (0.01-0.08Hz) in native space. To further reduce movement artifacts which may compromise connectivity assessment, (*96*) we performed motion scrubbing in which volumes exceeding a 0.5mm frame-wise displacement threshold were removed, as well as one prior and two subsequent volumes. All included subjects had at least five minutes of resting-state fMRI remaining after scrubbing (*97*). Spatial smoothing was not carried out to avoid artificially enhancing functional connectivity caused by signal spilling between adjacent brain regions. Pre-processed resting-state-fMRI images were subsequently warped to MNI space using the CAT12-derived spatial normalization parameters.

Assessment of tau epicenters and functional connectivity

Tau epicenters were determined for each subject as 5% of the 200 cortical Schaefer ROIs with highest baseline tau-PET SUVRs which is equivalent to 10 ROIs per individual. Subject-specific functional connectivity matrices were determined across the 200 ROIs of the Schaefer atlas as Fisher-z-transformed Pearson moment correlations between ROI-specific time-series. Negative correlations were eliminated, and autocorrelations were set to zero. Subject-specific tau epicenter masks were applied to the subject-specific functional connectivity matrices to determine average seed-based connectivity patterns of the tau epicenter to the rest of the brain. The tau epicenter to ROI connectivity per subject can be found in supplementary data files S1&S2 for ADNI and A4.

Statistics

Sample demographics for ADNI and A4 were compared using ANOVAs for continuous variables and Chi-squared tests for categorical variables. To determine the effect of Aβ on seed-based connectivity of the tau epicenter, we used linear regressions to determine the effect of regional Aβ (defined as the average centiloid across the tau epicenter and the target ROI) on

hat gelöscht: (i.e., EPI)
hat gelöscht: motion corrected (i.e.,
hat gelöscht:) and
hat gelöscht: registered
hat gelöscht: their
hat gelöscht: (i.e.,
hat gelöscht: timeseries
hat gelöscht:)
hat gelöscht: and applied
hat gelöscht: EPI
Feldfunktion geändert
Feldfunktion geändert
hat gelöscht: (i.e. tau maxima, overall 10 ROIs per subject)
hat gelöscht: eliminated
hat gelöscht: ¶ ... [3]
hat gelöscht: (i.e.
hat gelöscht: averaged
hat gelöscht:

epicenter connectivity, controlling for age, sex, ethnicity, MRI scanner type, diagnosis and framewise displacement. This analysis was conducted for ADNI and A4. ROI-wise p-values were FDR-corrected for multiple comparisons. In ADNI, we also applied a t-test against zero on the overall distribution of beta values, to determine whether there is a global association between Aβ and increased epicenter connectivity.

Next, we tested whether higher epicenter connectivity is linked to faster tau accumulation in the ADNI dataset with available longitudinal tau-PET data. To this end, we performed linear regression per ROI, testing the effect of tau epicenter connectivity at baseline on longitudinal tau-PET change rates, controlling for age, sex, ethnicity, diagnosis, MRI scanner type and average motion during the resting-state fMRI scan defined as the mean framewise displacement. ROI-wise p-values were FDR-corrected for multiple comparisons. Again, we applied a one-sample t-test to the beta-values to determine the global pattern of associations. Lastly, we employed bootstrapped mediation analyses with 1000 iterations per ROI, to assess whether the effect of Aβ on tau accumulation rates was mediated by stronger connectivity to the tau epicenter. Mediation models were again controlled for age, sex, ethnicity, diagnosis, MRI scanner type and average motion during the resting-state fMRI scan. All analyses were conducted for epicenter connectivity to all cortical ROIs and resulting beta and p-values were FDR-corrected for multiple comparisons. All statistical analyses were conducted using R statistical software (Version 4.0.4.). All plots have been created using ggplot2. Error bars in scatterplots indicate 95% confidence intervals of regression lines. In boxplots, the boxes indicate median±interquartile range, whiskers extend to values ±2.5 of the interquartile range from the median.

hat gelöscht: (i.e.

hat gelöscht:)

hat gelöscht: For post-mortem analyses, group comparisons were determined using two-sample t-tests.

References

1. C. R. Jack, Jr., D. M. Holtzman, Biomarker modeling of Alzheimer's disease. *Neuron* **80**, 1347-1358 (2013); published online EpubDec 18 (10.1016/j.neuron.2013.12.003).
2. N. Franzmeier, A. Dewenter, L. Frontzkowski, M. Dichgans, A. Rubinski, J. Neitzel, R. Smith, O. Strandberg, R. Ossenkoppele, K. Buerger, M. Duering, O. Hansson, M. Ewers, Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease. *Sci Adv* **6**, (2020); published online EpubNov (10.1126/sciadv.abd1327).
3. N. Franzmeier, J. Neitzel, A. Rubinski, R. Smith, O. Strandberg, R. Ossenkoppele, O. Hansson, M. Ewers, I. Alzheimer's Disease Neuroimaging, Functional brain architecture is associated with the rate of tau accumulation in Alzheimer's disease. *Nat Commun* **11**, 347 (2020); published online EpubJan 17 (10.1038/s41467-019-14159-1).
4. V. L. Villemagne, S. Burnham, P. Bourgeat, B. Brown, K. A. Ellis, O. Salvado, C. Szoeke, S. L. Macaulay, R. Martins, P. Maruff, D. Ames, C. C. Rowe, C. L. Masters, B. Australian Imaging, G. Lifestyle Research, Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol* **12**, 357-367 (2013); published online EpubApr (10.1016/S1474-4422(13)70044-9).
5. R. J. Bateman, C. Xiong, T. L. Benzinger, A. M. Fagan, A. Goate, N. C. Fox, D. S. Marcus, N. J. Cairns, X. Xie, T. M. Blazey, D. M. Holtzman, A. Santacruz, V. Buckles, A. Oliver, K. Moulder, P. S. Aisen, B. Ghetti, W. E. Klunk, E. McDade, R. N. Martins, C. L. Masters, R. Mayeux, J. M. Ringman, M. N. Rossor, P. R. Schofield, R. A. Sperling, S. Salloway, J. C. Morris, N. Dominantly Inherited Alzheimer, Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* **367**, 795-804 (2012); published online EpubAug 30 (10.1056/NEJMoa1202753).
6. B. A. Gordon, T. M. Blazey, Y. Su, A. Hari-Raj, A. Dincer, S. Flores, J. Christensen, E. McDade, G. Wang, C. Xiong, N. J. Cairns, J. Hassenstab, D. S. Marcus, A. M. Fagan, C. R. Jack, Jr., R. C. Hornbeck, K. L. Paumier, B. M. Ances, S. B. Berman, A. M. Brickman, D. M. Cash, J. P. Chhatwal, S. Correia, S. Forster, N. C. Fox, N. R. Graff-Radford, C. la Fougere, J. Levin, C. L. Masters, M. N. Rossor, S. Salloway, A. J. Saykin, P. R. Schofield, P. M. Thompson, M. M. Weiner, D. M. Holtzman, M. E. Raichle, J. C. Morris, R. J. Bateman, T. L. S. Benzinger, Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study. *Lancet Neurol* **17**, 241-250 (2018); published online EpubMar (10.1016/S1474-4422(18)30028-0).
7. C. R. Jack, Jr., D. S. Knopman, W. J. Jagust, R. C. Petersen, M. W. Weiner, P. S. Aisen, L. M. Shaw, P. Vemuri, H. J. Wiste, S. D. Weigand, T. G. Lesnick, V. S. Pankratz, M. C. Donohue, J. Q. Trojanowski, Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* **12**, 207-216 (2013); published online EpubFeb (10.1016/S1474-4422(12)70291-0).
8. A. Goate, M. C. Chartier-Harlin, M. Mullan, J. Brown, F. Crawford, L. Fidani, L. Giuffra, A. Haynes, N. Irving, L. James, et al., Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* **349**, 704-706 (1991); published online EpubFeb 21 (10.1038/349704a0).

9. B. Ghetti, A. L. Oblak, B. F. Boeve, K. A. Johnson, B. C. Dickerson, M. Goedert, Invited review: Frontotemporal dementia caused by microtubule-associated protein tau gene (MAPT) mutations: a chameleon for neuropathology and neuroimaging. *Neuropathol Appl Neurobiol* **41**, 24-46 (2015); published online EpubFeb (10.1111/nan.12213).
10. D. A. Bennett, J. A. Schneider, Z. Arvanitakis, J. F. Kelly, N. T. Aggarwal, R. C. Shah, R. S. Wilson, Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology* **66**, 1837-1844 (2006); published online EpubJun 27 (10.1212/01.wnl.0000219668.47116.e6).
11. M. Scholl, S. N. Lockhart, D. R. Schonhaut, J. P. O'Neil, M. Janabi, R. Ossenkoppele, S. L. Baker, J. W. Vogel, J. Faria, H. D. Schwimmer, G. D. Rabinovici, W. J. Jagust, PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron* **89**, 971-982 (2016); published online EpubMar 2 (10.1016/j.neuron.2016.01.028).
12. A. Maass, S. Landau, S. L. Baker, A. Horng, S. N. Lockhart, R. La Joie, G. D. Rabinovici, W. J. Jagust, I. Alzheimer's Disease Neuroimaging, Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. *Neuroimage* **157**, 448-463 (2017); published online EpubAug 15 (10.1016/j.neuroimage.2017.05.058).
13. R. La Joie, A. V. Visani, S. L. Baker, J. A. Brown, V. Bourakova, J. Cha, K. Chaudhary, L. Edwards, L. Iaccarino, M. Janabi, O. H. Lesman-Segev, Z. A. Miller, D. C. Perry, J. P. O'Neil, J. Pham, J. C. Rojas, H. J. Rosen, W. W. Seeley, R. M. Tsai, B. L. Miller, W. J. Jagust, G. D. Rabinovici, Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci Transl Med* **12**, (2020); published online EpubJan 1 (10.1126/scitranslmed.aau5732).
14. D. Biel, M. Brendel, A. Rubinski, K. Buerger, D. Janowitz, M. Dichgans, N. Franzmeier, I. Alzheimer's Disease Neuroimaging, Tau-PET and in vivo Braak-staging as prognostic markers of future cognitive decline in cognitively normal to demented individuals. *Alzheimers Res Ther* **13**, 137 (2021); published online EpubAug 12 (10.1186/s13195-021-00880-x).
15. M. Jin, N. Shepardson, T. Yang, G. Chen, D. Walsh, D. J. Selkoe, Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. *Proc Natl Acad Sci U S A* **108**, 5819-5824 (2011); published online EpubApr 5 (10.1073/pnas.1017033108).
16. R. E. Bennett, S. L. DeVos, S. Dujardin, B. Corjuc, R. Gor, J. Gonzalez, A. D. Roe, M. P. Frosch, R. Pitstick, G. A. Carlson, B. T. Hyman, Enhanced Tau Aggregation in the Presence of Amyloid beta. *Am J Pathol* **187**, 1601-1612 (2017); published online EpubJul (10.1016/j.ajpath.2017.03.011).
17. S. Palmqvist, M. Schöll, O. Strandberg, N. Mattsson, E. Stomrud, H. Zetterberg, K. Blennow, S. Landau, W. Jagust, O. Hansson, Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nat Commun* **8**, 1214 (2017); published online EpubOct 31 (10.1038/s41467-017-01150-x).
18. D. R. Thal, U. Rüb, M. Orantes, H. Braak, Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* **58**, 1791-1800 (2002); published online EpubJun 25 (10.1212/wnl.58.12.1791).
19. M. J. Grothe, H. Barthel, J. Sepulcre, M. Dyrba, O. Sabri, S. J. Teipel, I. Alzheimer's Disease Neuroimaging, In vivo staging of regional amyloid deposition. *Neurology* **89**,

2031-2038 (2017); published online EpubNov 14 (10.1212/WNL.0000000000004643).
20. H. Braak, E. Braak, Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* **82**, 239-259 (1991)10.1007/bf00308809).
21. M. Schöll, S. N. Lockhart, D. R. Schonhaut, J. P. O'Neil, M. Janabi, R. Ossenkoppele, S. L. Baker, J. W. Vogel, J. Faria, H. D. Schwimmer, G. D. Rabinovici, W. J. Jagust, PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron* **89**, 971-982 (2016); published online EpubMar 2 (10.1016/j.neuron.2016.01.028).
22. A. Wuestefeld, A. Pichet Binette, D. Berron, N. Spotorno, D. van Westen, E. Stomrud, N. Mattsson-Carlgren, O. Strandberg, R. Smith, S. Palmqvist, T. Glenn, S. Moes, M. Honer, K. Arfanakis, L. L. Barnes, D. A. Bennett, J. A. Schneider, L. E. M. Wisse, O. Hansson, Age-related and amyloid-beta-independent tau deposition and its downstream effects. *Brain* **146**, 3192-3205 (2023); published online EpubAug 1 (10.1093/brain/awad135).
23. J. F. Crary, J. Q. Trojanowski, J. A. Schneider, J. F. Abisambra, E. L. Abner, I. Alafuzoff, S. E. Arnold, J. Attems, T. G. Beach, E. H. Bigio, N. J. Cairns, D. W. Dickson, M. Gearing, L. T. Grinberg, P. R. Hof, B. T. Hyman, K. Jellinger, G. A. Jicha, G. G. Kovacs, D. S. Knopman, J. Kofler, W. A. Kukull, I. R. Mackenzie, E. Masliah, A. McKee, T. J. Montine, M. E. Murray, J. H. Neltner, I. Santa-Maria, W. W. Seeley, A. Serrano-Pozo, M. L. Shelanski, T. Stein, M. Takao, D. R. Thal, J. B. Toledo, J. C. Troncoso, J. P. Vonsattel, C. L. White, 3rd, T. Wisniewski, R. L. Woltjer, M. Yamada, P. T. Nelson, Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol* **128**, 755-766 (2014); published online EpubDec (10.1007/s00401-014-1349-0).
24. J. W. Wu, S. A. Hussaini, I. M. Bastille, G. A. Rodriguez, A. Mrejeru, K. Rilett, D. W. Sanders, C. Cook, H. Fu, R. A. Boonen, M. Herman, E. Nahmani, S. Emrani, Y. H. Figueroa, M. I. Diamond, C. L. Clelland, S. Wray, K. E. Duff, Neuronal activity enhances tau propagation and tau pathology in vivo. *Nat Neurosci* **19**, 1085-1092 (2016); published online EpubAug (10.1038/nn.4328).
25. J. W. Vogel, N. Corriveau-Lecavalier, N. Franzmeier, J. B. Pereira, J. A. Brown, A. Maass, H. Botha, W. W. Seeley, D. S. Bassett, D. T. Jones, M. Ewers, Connectome-based modelling of neurodegenerative diseases: towards precision medicine and mechanistic insight. *Nat Rev Neurosci* **24**, 620-639 (2023); published online EpubOct (10.1038/s41583-023-00731-8).
26. M. Merezhko, R. L. Uronen, H. J. Huttunen, The Cell Biology of Tau Secretion. *Front Mol Neurosci* **13**, 569818 (2020)10.3389/fnmol.2020.569818).
27. A. M. Pooler, E. C. Phillips, D. H. Lau, W. Noble, D. P. Hanger, Physiological release of endogenous tau is stimulated by neuronal activity. *EMBO Rep* **14**, 389-394 (2013); published online EpubApr (10.1038/embor.2013.15).
28. N. Franzmeier, J. Neitzel, A. Rubinski, R. Smith, O. Strandberg, R. Ossenkoppele, O. Hansson, M. Ewers, Functional brain architecture is associated with the rate of tau accumulation in Alzheimer's disease. *Nat Commun* **11**, 347 (2020); published online EpubJan 17 (10.1038/s41467-019-14159-1).
29. L. Frontzkowski, M. Ewers, M. Brendel, D. Biel, R. Ossenkoppele, P. Hager, A. Steward, A. Dewenter, S. Römer, A. Rubinski, K. Buerger, D. Janowitz, A. P. Binette, R. Smith, O. Strandberg, N. M. Carlgren, M. Dichgans, O. Hansson, N. Franzmeier, Earlier Alzheimer's disease onset is associated with tau pathology in brain hub

regions and facilitated tau spreading. *Nat Commun* **13**, 4899 (2022); published online EpubAug 20 (10.1038/s41467-022-32592-7).
30. A. Pichet Binette, N. Franzmeier, N. Spotorno, M. Ewers, M. Brendel, D. Biel, O. Strandberg, S. Janelidze, S. Palmqvist, N. Mattsson-Carlgren, R. Smith, E. Stomrud, R. Ossenkoppele, O. Hansson, Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. *Nat Commun* **13**, 6635 (2022); published online EpubNov 4 (10.1038/s41467-022-34129-4).
31. A. Steward, D. Biel, M. Brendel, A. Dewenter, S. Roemer, A. Rubinski, Y. Luan, M. Dichgans, M. Ewers, N. Franzmeier, Functional network segregation is associated with attenuated tau spreading in Alzheimer's disease. *Alzheimers Dement* **19**, 2034-2046 (2023); published online EpubMay (10.1002/alz.12867).
32. A. Steward, D. Biel, A. Dewenter, S. Roemer, F. Wagner, A. Dehsarvi, S. Rathore, D. Otero Svaldi, I. Higgins, M. Brendel, M. Dichgans, S. Shcherbinin, M. Ewers, N. Franzmeier, ApoE4 and Connectivity-Mediated Spreading of Tau Pathology at Lower Amyloid Levels. *JAMA Neurol*, (2023); published online EpubNov 6 (10.1001/jamaneurol.2023.4038).
33. D. N. Schoonhoven, E. M. Coomans, A. P. Millan, A. M. van Nifterick, D. Visser, R. Ossenkoppele, H. Tuncel, W. M. van der Flier, S. S. V. Golla, P. Scheltens, A. Hillebrand, B. N. M. van Berckel, C. J. Stam, A. A. Gouw, Tau protein spreads through functionally connected neurons in Alzheimer's disease: a combined MEG/PET study. *Brain* **146**, 4040-4054 (2023); published online EpubOct 3 (10.1093/brain/awad189).
34. I. Sintini, J. Graff-Radford, D. T. Jones, H. Botha, P. R. Martin, M. M. Machulda, C. G. Schwarz, M. L. Senjem, J. L. Gunter, C. R. Jack, V. J. Lowe, K. A. Josephs, J. L. Whitwell, Tau and Amyloid Relationships with Resting-state Functional Connectivity in Atypical Alzheimer's Disease. *Cereb Cortex* **31**, 1693-1706 (2021); published online EpubFeb 5 (10.1093/cercor/bhaa319).
35. R. Ossenkoppele, L. Iaccarino, D. R. Schonhaut, J. A. Brown, R. La Joie, J. P. O'Neil, M. Janabi, S. L. Baker, J. H. Kramer, M. L. Gorno-Tempini, B. L. Miller, H. J. Rosen, W. W. Seeley, W. J. Jagust, G. D. Rabinovici, Tau covariance patterns in Alzheimer's disease patients match intrinsic connectivity networks in the healthy brain. *Neuroimage Clin* **23**, 101848 (2019)10.1016/j.nicl.2019.101848).
36. J. J. Palop, L. Mucke, Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. *Nat Neurosci* **13**, 812-818 (2010); published online EpubJul (10.1038/nn.2583).
37. R. Minkeviciene, S. Rheims, M. B. Dobszay, M. Zilberter, J. Hartikainen, L. Fülöp, B. Penke, Y. Zilberter, T. Harkany, A. Pitkänen, H. Tanila, Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy. *J Neurosci* **29**, 3453-3462 (2009); published online EpubMar 18 (10.1523/jneurosci.5215-08.2009).
38. D. L. Vogt, D. Thomas, V. Galvan, D. E. Bredesen, B. T. Lamb, S. W. Pimplikar, Abnormal neuronal networks and seizure susceptibility in mice overexpressing the APP intracellular domain. *Neurobiol Aging* **32**, 1725-1729 (2011); published online EpubSep (10.1016/j.neurobiolaging.2009.09.002).
39. M. A. Busche, X. Chen, H. A. Henning, J. Reichwald, M. Staufenbiel, B. Sakmann, A. Konnerth, Critical role of soluble amyloid-beta for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **109**, 8740-8745 (2012); published online EpubMay 29 (10.1073/pnas.1206171109).

40. M. A. Busche, G. Eichhoff, H. Adelsberger, D. Abramowski, K. H. Wiederhold, C. Haass, M. Staufenbiel, A. Konnerth, O. Garaschuk, Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science* **321**, 1686-1689 (2008); published online EpubSep 19 (10.1126/science.1162844).
41. I. R. H. Ben-Nejma, A. J. Keliris, J. Daans, P. Ponsaerts, M. Verhoye, A. Van der Linden, G. A. Keliris, Increased soluble amyloid-beta causes early aberrant brain network hypersynchronisation in a mature-onset mouse model of amyloidosis. *Acta Neuropathol Commun* **7**, 180 (2019); published online EpubNov 14 (10.1186/s40478-019-0810-7).
42. S. Li, S. Hong, N. E. Shepardson, D. M. Walsh, G. M. Shankar, D. Selkoe, Soluble oligomers of amyloid Beta protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. *Neuron* **62**, 788-801 (2009); published online EpubJun 25 (10.1016/j.neuron.2009.05.012).
43. Z. Wu, Z. Guo, M. Gearing, G. Chen, Tonic inhibition in dentate gyrus impairs long-term potentiation and memory in an Alzheimer's [corrected] disease model. *Nat Commun* **5**, 4159 (2014); published online EpubJun 13 (10.1038/ncomms5159).
44. A. D. Lam, R. A. Sarkis, K. R. Pellerin, J. Jing, B. A. Dworetzky, D. B. Hoch, C. S. Jacobs, J. W. Lee, D. S. Weisholtz, R. Zepeda, M. B. Westover, A. J. Cole, S. S. Cash, Association of epileptiform abnormalities and seizures in Alzheimer disease. *Neurology* **95**, e2259-e2270 (2020); published online EpubOct 20 (10.1212/WNL.0000000000010612).
45. D. Shah, J. Praet, A. Latif Hernandez, C. Hofling, C. Anckaerts, F. Bard, M. Morawski, J. R. Detrez, E. Prinsen, A. Villa, W. H. De Vos, A. Maggi, R. D'Hooge, D. Balschun, S. Rossner, M. Verhoye, A. Van der Linden, Early pathologic amyloid induces hypersynchrony of BOLD resting-state networks in transgenic mice and provides an early therapeutic window before amyloid plaque deposition. *Alzheimers Dement* **12**, 964-976 (2016); published online EpubSep (10.1016/j.jalz.2016.03.010).
46. A. P. Schultz, J. P. Chhatwal, T. Hedden, E. C. Mormino, B. J. Hanseeuw, J. Sepulcre, W. Huijbers, M. LaPoint, R. F. Buckley, K. A. Johnson, R. A. Sperling, Phases of Hyperconnectivity and Hypoconnectivity in the Default Mode and Salience Networks Track with Amyloid and Tau in Clinically Normal Individuals. *J Neurosci* **37**, 4323-4331 (2017); published online EpubApr 19 (10.1523/JNEUROSCI.3263-16.2017).
47. S. Palmqvist, M. Scholl, O. Strandberg, N. Mattsson, E. Stomrud, H. Zetterberg, K. Blennow, S. Landau, W. Jagust, O. Hansson, Earliest accumulation of beta-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nat Commun* **8**, 1214 (2017); published online EpubOct 31 (10.1038/s41467-017-01150-x).
48. B. C. Dickerson, D. H. Salat, D. N. Greve, E. F. Chua, E. Rand-Giovannetti, D. M. Rentz, L. Bertram, K. Mullin, R. E. Tanzi, D. Blacker, M. S. Albert, R. A. Sperling, Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* **65**, 404-411 (2005); published online EpubAug 9 (10.1212/01.wnl.0000171450.97464.49).
49. W. Huijbers, E. C. Mormino, A. P. Schultz, S. Wigman, A. M. Ward, M. Larvie, R. E. Amariglio, G. A. Marshall, D. M. Rentz, K. A. Johnson, R. A. Sperling, Amyloid-beta deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. *Brain* **138**, 1023-1035 (2015); published online EpubApr (10.1093/brain/awv007).

50. J. Giorgio, J. N. Adams, A. Maass, W. J. Jagust, M. Breakspear, Amyloid induced hyperexcitability in default mode network drives medial temporal hyperactivity and early tau accumulation. *Neuron* **112**, 676-686 e674 (2024); published online EpubFeb 21 (10.1016/j.neuron.2023.11.014).
51. D. Jones, V. Lowe, J. Graff-Radford, H. Botha, L. Barnard, D. Wiepert, M. C. Murphy, M. Murray, M. Senjem, J. Gunter, H. Wiste, B. Boeve, D. Knopman, R. Petersen, C. Jack, A computational model of neurodegeneration in Alzheimer's disease. *Nat Commun* **13**, 1643 (2022); published online EpubMar 28 (10.1038/s41467-022-29047-4).
52. D. T. Jones, J. Graff-Radford, V. J. Lowe, H. J. Wiste, J. L. Gunter, M. L. Senjem, H. Botha, K. Kantarci, B. F. Boeve, D. S. Knopman, R. C. Petersen, C. R. Jack, Jr., Tau, amyloid, and cascading network failure across the Alzheimer's disease spectrum. *Cortex* **97**, 143-159 (2017); published online EpubDec (10.1016/j.cortex.2017.09.018).
53. D. T. Jones, D. S. Knopman, J. L. Gunter, J. Graff-Radford, P. Vemuri, B. F. Boeve, R. C. Petersen, M. W. Weiner, C. R. Jack, Jr., I. Alzheimer's Disease Neuroimaging, Cascading network failure across the Alzheimer's disease spectrum. *Brain* **139**, 547-562 (2016); published online EpubFeb (10.1093/brain/awv338).
54. D. A. Wiepert, V. J. Lowe, D. S. Knopman, B. F. Boeve, J. Graff-Radford, R. C. Petersen, C. R. Jack, Jr., D. T. Jones, A robust biomarker of large-scale network failure in Alzheimer's disease. *Alzheimers Dement (Amst)* **6**, 152-161 (2017)10.1016/j.dadm.2017.01.004).
55. J. Voglein, I. Ricard, S. Noachtar, W. A. Kukull, M. Dieterich, J. Levin, A. Danek, Seizures in Alzheimer's disease are highly recurrent and associated with a poor disease course. *J Neurol* **267**, 2941-2948 (2020); published online EpubOct (10.1007/s00415-020-09937-7).
56. K. A. Vossel, A. J. Beagle, G. D. Rabinovici, H. Shu, S. E. Lee, G. Naasan, M. Hegde, S. B. Cornes, M. L. Henry, A. B. Nelson, W. W. Seeley, M. D. Geschwind, M. L. Gorno-Tempini, T. Shih, H. E. Kirsch, P. A. Garcia, B. L. Miller, L. Mucke, Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurol* **70**, 1158-1166 (2013); published online EpubSep 1 (10.1001/jamaneurol.2013.136).
57. E. A. Csernus, T. Werber, A. Kamondi, A. A. Horvath, The Significance of Subclinical Epileptiform Activity in Alzheimer's Disease: A Review. *Front Neurol* **13**, 856500 (2022)10.3389/fneur.2022.856500).
58. K. A. Vossel, K. G. Ranasinghe, A. J. Beagle, D. Mizuiri, S. M. Honma, A. F. Dowling, S. M. Darwish, V. Van Berlo, D. E. Barnes, M. Mantle, A. M. Karydas, G. Coppola, E. D. Roberson, B. L. Miller, P. A. Garcia, H. E. Kirsch, L. Mucke, S. S. Nagarajan, Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann Neurol* **80**, 858-870 (2016); published online EpubDec (10.1002/ana.24794).
59. A. D. Lam, G. Deck, A. Goldman, E. N. Eskandar, J. Noebels, A. J. Cole, Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. *Nat Med* **23**, 678-680 (2017); published online EpubJun (10.1038/nm.4330).
60. K. Yamada, J. K. Holth, F. Liao, F. R. Stewart, T. E. Mahan, H. Jiang, J. R. Cirrito, T. K. Patel, K. Hochgrafe, E. M. Mandelkow, D. M. Holtzman, Neuronal activity regulates extracellular tau in vivo. *J Exp Med* **211**, 387-393 (2014); published online EpubMar 10 (10.1084/jem.20131685).

61. G. A. Rodriguez, G. M. Barrett, K. E. Duff, S. A. Hussaini, Chemogenetic attenuation of neuronal activity in the entorhinal cortex reduces Abeta and tau pathology in the hippocampus. *PLoS Biol* **18**, e3000851 (2020); published online EpubAug (10.1371/journal.pbio.3000851).
62. A. Schaefer, R. Kong, E. M. Gordon, T. O. Laumann, X. N. Zuo, A. J. Holmes, S. B. Eickhoff, B. T. T. Yeo, Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex* **28**, 3095-3114 (2018); published online EpubSep 1 (10.1093/cercor/bhx179).
63. A. Leuzy, K. Chiotis, L. Lemoine, P. G. Gillberg, O. Almkvist, E. Rodriguez-Vieitez, A. Nordberg, Tau PET imaging in neurodegenerative tauopathies-still a challenge. *Mol Psychiatry* **24**, 1112-1134 (2019); published online EpubAug (10.1038/s41380-018-0342-8).
64. W. E. Klunk, R. A. Koeppe, J. C. Price, T. L. Benzinger, M. D. Devous, Sr., W. J. Jagust, K. A. Johnson, C. A. Mathis, D. Minhas, M. J. Pontecorvo, C. C. Rowe, D. M. Skovronsky, M. A. Mintun, The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement* **11**, 1-15 e11-14 (2015); published online EpubJan (10.1016/j.jalz.2014.07.003).
65. A. Pichet Binette, N. Franzmeier, N. Spotorno, M. Ewers, M. Brendel, D. Biel, I. Alzheimer's Disease Neuroimaging, O. Strandberg, S. Janelidze, S. Palmqvist, N. Mattsson-Carlgren, R. Smith, E. Stomrud, R. Ossenkoppele, O. Hansson, Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. *Nat Commun* **13**, 6635 (2022); published online EpubNov 4 (10.1038/s41467-022-34129-4).
66. M. Scholl, A. Maass, N. Mattsson, N. J. Ashton, K. Blennow, H. Zetterberg, W. Jagust, Biomarkers for tau pathology. *Mol Cell Neurosci* **97**, 18-33 (2019); published online EpubJun (10.1016/j.mcn.2018.12.001).
67. O. Langford, R. Raman, R. A. Sperling, J. Cummings, C. K. Sun, G. Jimenez-Maggiora, P. S. Aisen, M. C. Donohue, Predicting Amyloid Burden to Accelerate Recruitment of Secondary Prevention Clinical Trials. *J Prev Alzheimers Dis* **7**, 213-218 (2020)10.14283/jpad.2020.44).
68. X. Tang, D. Wu, L. H. Gu, B. B. Nie, X. Y. Qi, Y. J. Wang, F. F. Wu, X. L. Li, F. Bai, X. C. Chen, L. Xu, Q. G. Ren, Z. J. Zhang, Spatial learning and memory impairments are associated with increased neuronal activity in 5XFAD mouse as measured by manganese-enhanced magnetic resonance imaging. *Oncotarget* **7**, 57556-57570 (2016); published online EpubSep 6 (10.18632/oncotarget.11353).
69. W. J. Lee, J. A. Brown, H. R. Kim, R. La Joie, H. Cho, C. H. Lyoo, G. D. Rabinovici, J. K. Seong, W. W. Seeley, I. Alzheimer's Disease Neuroimaging, Regional Abeta-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading. *Neuron* **110**, 1932-1943 e1935 (2022); published online EpubJun 15 (10.1016/j.neuron.2022.03.034).
70. C. Costa, M. Romoli, C. Liguori, L. Farotti, P. Eusebi, C. Bedetti, S. Siliquini, E. N. Cesarini, A. Romigi, N. B. Mercuri, L. Parnetti, P. Calabresi, Alzheimer's disease and late-onset epilepsy of unknown origin: two faces of beta amyloid pathology. *Neurobiol Aging* **73**, 61-67 (2019); published online EpubJan (10.1016/j.neurobiolaging.2018.09.006).
71. N. Franzmeier, A. Rubinski, J. Neitzel, Y. Kim, A. Damm, D. L. Na, H. J. Kim, C. H. Lyoo, H. Cho, S. Finsterwalder, M. Duering, S. W. Seo, M. Ewers, I. Alzheimer's Disease

Neuroimaging, Functional connectivity associated with tau levels in ageing, Alzheimer's, and small vessel disease. *Brain* **142**, 1093-1107 (2019); published online EpubApr 1 (10.1093/brain/awz026).

72. R. Ossenkoppele, A. Pichet Binette, C. Groot, R. Smith, O. Strandberg, S. Palmqvist, E. Stomrud, P. Tideman, T. Ohlsson, J. Jogi, K. Johnson, R. Sperling, V. Dore, C. L. Masters, C. Rowe, D. Visser, B. N. M. van Berckel, W. M. van der Flier, S. Baker, W. J. Jagust, H. J. Wiste, R. C. Petersen, C. R. Jack, Jr., O. Hansson, Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nat Med* **28**, 2381-2387 (2022); published online EpubNov (10.1038/s41591-022-02049-x).
73. A. Hahn, T. O. Strandberg, E. Stomrud, M. Nilsson, D. van Westen, S. Palmqvist, R. Ossenkoppele, O. Hansson, Association Between Earliest Amyloid Uptake and Functional Connectivity in Cognitively Unimpaired Elderly. *Cereb Cortex* **29**, 2173-2182 (2019); published online EpubMay 1 (10.1093/cercor/bhz020).
74. D. Park, M. Na, J. A. Kim, U. Lee, E. Cho, M. Jang, S. Chang, Activation of CaMKIV by soluble amyloid-beta(1-42) impedes trafficking of axonal vesicles and impairs activity-dependent synaptogenesis. *Sci Signal* **10**, (2017); published online EpubJul 11 (10.1126/scisignal.aam8661).
75. S. Q. Ren, W. Yao, J. Z. Yan, C. Jin, J. J. Yin, J. Yuan, S. Yu, Z. Cheng, Amyloid beta causes excitation/inhibition imbalance through dopamine receptor 1-dependent disruption of fast-spiking GABAergic input in anterior cingulate cortex. *Sci Rep* **8**, 302 (2018); published online EpubJan 10 (10.1038/s41598-017-18729-5).
76. A. M. van Nifterick, A. A. Gouw, R. E. van Kesteren, P. Scheltens, C. J. Stam, W. de Haan, A multiscale brain network model links Alzheimer's disease-mediated neuronal hyperactivity to large-scale oscillatory slowing. *Alzheimers Res Ther* **14**, 101 (2022); published online EpubJul 25 (10.1186/s13195-022-01041-4).
77. S. Niraula, J. J. Doderer, S. Indulkar, K. P. Berry, W. L. Hauser, O. J. L'Esperance, J. Z. Deng, G. Keeter, A. G. Rouse, J. Subramanian, Excitation-inhibition imbalance disrupts visual familiarity in amyloid and non-pathology conditions. *Cell Rep* **42**, 111946 (2023); published online EpubJan 31 (10.1016/j.celrep.2022.111946).
78. H. S. Moon, H. Jiang, T. T. Vo, W. B. Jung, A. L. Vazquez, S. G. Kim, Contribution of Excitatory and Inhibitory Neuronal Activity to BOLD fMRI. *Cereb Cortex* **31**, 4053-4067 (2021); published online EpubJul 29 (10.1093/cercor/bhab068).
79. L. Liu, V. Drouet, J. W. Wu, M. P. Witter, S. A. Small, C. Clelland, K. Duff, Trans-synaptic spread of tau pathology in vivo. *PLoS One* **7**, e31302 (2012)10.1371/journal.pone.0031302).
80. Y. Wang, V. Balaji, S. Kaniyappan, L. Kruger, S. Irsen, K. Tepper, R. Chandupatla, W. Maetzler, A. Schneider, E. Mandelkow, E. M. Mandelkow, The release and trans-synaptic transmission of Tau via exosomes. *Mol Neurodegener* **12**, 5 (2017); published online EpubJan 13 (10.1186/s13024-016-0143-y).
81. E. S. Finn, X. Shen, D. Scheinost, M. D. Rosenberg, J. Huang, M. M. Chun, X. Papademetris, R. T. Constable, Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci* **18**, 1664-1671 (2015); published online EpubNov (10.1038/nn.4135).
82. J. W. Vogel, A. L. Young, N. P. Oxtoby, R. Smith, R. Ossenkoppele, O. T. Strandberg, R. La Joie, L. M. Aksman, M. J. Grothe, Y. Iturria-Medina, I. Alzheimer's Disease Neuroimaging, M. J. Pontecorvo, M. D. Devous, G. D. Rabinovici, D. C. Alexander, C.

H. Lyoo, A. C. Evans, O. Hansson, Four distinct trajectories of tau deposition identified in Alzheimer's disease. *Nat Med* **27**, 871-881 (2021); published online EpubMay (10.1038/s41591-021-01309-6).

83. A. Steward, D. Biel, M. Brendel, A. Dewenter, S. Roemer, A. Rubinski, Y. Luan, M. Dichgans, M. Ewers, N. Franzmeier, I. Alzheimer's Disease Neuroimaging, Functional network segregation is associated with attenuated tau spreading in Alzheimer's disease. *Alzheimers Dement* **19**, 2034-2046 (2023); published online EpubMay (10.1002/alz.12867).
84. M. Wirth, M. Gaubert, T. Kobe, A. Garnier-Crussard, C. Lange, J. Gonneaud, R. de Flores, B. Landeau, V. de la Sayette, G. Chetelat, Vascular Health Is Associated With Functional Connectivity Decline in Higher-Order Networks of Older Adults. *Front Integr Neurosci* **16**, 847824 (2022)10.3389/fnint.2022.847824).
85. L. Passamonti, K. A. Tsvetanov, P. S. Jones, W. R. Bevan-Jones, R. Arnold, R. J. Borchert, E. Mak, L. Su, J. T. O'Brien, J. B. Rowe, Neuroinflammation and Functional Connectivity in Alzheimer's Disease: Interactive Influences on Cognitive Performance. *J Neurosci* **39**, 7218-7226 (2019); published online EpubSep 4 (10.1523/JNEUROSCI.2574-18.2019).
86. C. Sato, N. R. Barthelemy, K. G. Mawuenyega, B. W. Patterson, B. A. Gordon, J. Jockel-Balsarotti, M. Sullivan, M. J. Crisp, T. Kasten, K. M. Kirmess, N. M. Kanaan, K. E. Yarasheski, A. Baker-Nigh, T. L. S. Benzinger, T. M. Miller, C. M. Karch, R. J. Bateman, Tau Kinetics in Neurons and the Human Central Nervous System. *Neuron* **97**, 1284-1298 e1287 (2018); published online EpubMar 21 (10.1016/j.neuron.2018.02.015).
87. H. Y. Wu, P. C. Kuo, Y. T. Wang, H. T. Lin, A. D. Roe, B. Y. Wang, C. L. Han, B. T. Hyman, Y. J. Chen, H. C. Tai, beta-Amyloid Induces Pathology-Related Patterns of Tau Hyperphosphorylation at Synaptic Terminals. *J Neuropathol Exp Neurol* **77**, 814-826 (2018); published online EpubSep 1 (10.1093/jnen/nly059).
88. H. Huang, M. Ding, Linking Functional Connectivity and Structural Connectivity Quantitatively: A Comparison of Methods. *Brain Connect* **6**, 99-108 (2016); published online EpubMar (10.1089/brain.2015.0382).
89. T. A. Engel, M. L. Scholvinck, C. M. Lewis, The diversity and specificity of functional connectivity across spatial and temporal scales. *Neuroimage* **245**, 118692 (2021); published online EpubDec 15 (10.1016/j.neuroimage.2021.118692).
90. K. A. Vossel, M. C. Tartaglia, H. B. Nygaard, A. Z. Zeman, B. L. Miller, Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol* **16**, 311-322 (2017); published online EpubApr (10.1016/s1474-4422(17)30044-3).
91. D. Biel, Y. Luan, M. Brendel, P. Hager, A. Dewenter, A. Moscoso, D. Otero Svaldi, I. A. Higgins, M. Pontecorvo, S. Romer, A. Steward, A. Rubinski, L. Zheng, M. Scholl, S. Shcherbinin, M. Ewers, N. Franzmeier, I. Alzheimer's Disease Neuroimaging, Combining tau-PET and fMRI meta-analyses for patient-centered prediction of cognitive decline in Alzheimer's disease. *Alzheimers Res Ther* **14**, 166 (2022); published online EpubNov 7 (10.1186/s13195-022-01105-5).
92. S. M. Landau, M. A. Mintun, A. D. Joshi, R. A. Koeppe, R. C. Petersen, P. S. Aisen, M. W. Weiner, W. J. Jagust, I. Alzheimer's Disease Neuroimaging, Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol* **72**, 578-586 (2012); published online EpubOct (10.1002/ana.23650).
93. S. K. Royse, D. S. Minhas, B. J. Lopresti, A. Murphy, T. Ward, R. A. Koeppe, S. Bullich, S. DeSanti, W. J. Jagust, S. M. Landau, I. Alzheimer's Disease Neuroimaging,

Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. *Alzheimers Res Ther* **13**, 99 (2021); published online EpubMay 10 (10.1186/s13195-021-00836-1).

94. S. L. Baker, A. Maass, W. J. Jagust, Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data. *Data Brief* **15**, 648-657 (2017); published online EpubDec (10.1016/j.dib.2017.10.024).

95. N. Franzmeier, M. Duering, M. Weiner, M. Dichgans, M. Ewers, I. Alzheimer's Disease Neuroimaging, Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. *Neurology* **88**, 1054-1061 (2017); published online EpubMar 14 (10.1212/WNL.0000000000003711).

96. J. D. Power, A. Mitra, T. O. Laumann, A. Z. Snyder, B. L. Schlaggar, S. E. Petersen, Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* **84**, 320-341 (2014); published online EpubJan 1 (10.1016/j.neuroimage.2013.08.048).

97. N. Franzmeier, E. Düzel, F. Jessen, K. Buerger, J. Levin, M. Duering, M. Dichgans, C. Haass, M. Suárez-Calvet, A. M. Fagan, K. Paumier, T. Benzinger, C. L. Masters, J. C. Morris, R. Perneczky, D. Janowitz, C. Catak, S. Wolfsgruber, M. Wagner, S. Teipel, I. Kilimann, A. Ramirez, M. Rossor, M. Jucker, J. Chhatwal, A. Spottke, H. Boecker, F. Brosseron, P. Falkai, K. Fliessbach, M. T. Heneka, C. Laske, P. Nestor, O. Peters, M. Fuentes, F. Menne, J. Priller, E. J. Spruth, C. Franke, A. Schneider, B. Kofler, C. Westerteicher, O. Speck, J. Wiltfang, C. Bartels, M. Araque Caballero, C. Metzger, D. Bittner, M. Weiner, J. H. Lee, S. Salloway, A. Danek, A. Goate, P. R. Schofield, R. J. Bateman, M. Ewers, Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. *Brain* **141**, 1186-1200 (2018); published online EpubApr 1 (10.1093/brain/awy008).

ACKNOWLEDGEMENTS

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

The A4 Study was a secondary prevention trial in preclinical Alzheimer's disease, aiming to slow cognitive decline associated with brain amyloid accumulation in clinically normal older individuals. The A4 Study was funded by a public-private-philanthropic partnership, including funding from the National Institutes of Health-National Institute on Aging, Eli Lilly and Company, Alzheimer's Association, Accelerating Medicines Partnership, GHR Foundation, an anonymous foundation, and additional private donors, with in-kind support from Avid Radiopharmaceuticals, Cogstate, Albert Einstein College of Medicine and the Foundation for Neurologic Diseases.The companion observational Longitudinal Evaluation of Amyloid Risk

hat gelöscht: and/or

and Neurodegeneration (LEARN) Study was funded by the Alzheimer's Association and GHR Foundation. The A4 and LEARN Studies were led by Dr. Reisa Sperling at Brigham and Women's Hospital, Harvard Medical School, and Dr. Paul Aisen at the Alzheimer's Therapeutic Research Institute (ATRI) at the University of Southern California. The A4 and LEARN Studies were coordinated by ATRI at the University of Southern California, and the data are made available under the auspices of Alzheimer's Clinical Trial Consortium through the Global Research & Imaging Platform (GRIP). The complete A4 Study Team list is available on: https://www.actcinfo.org/a4-study-team-lists/. We would like to acknowledge the dedication of the study participants and their study partners who made the A4 and LEARN Studies possible.

Funding: This work was supported by grants of the Bright Focus Foundation (A2021026S to NF), Alzheimer's Association (AARG-22-973496 to NF) and the Gerhard and Ilse Schick Stiftung to NF.

Author contributions: S.N.R., F.W., L.E.: study concept and design, data analysis, drafting the manuscript. B.R., A.Dehsarvi., A.S., A.Dewenter., D.B., Z.Z., J.P., M.G. data processing, critical revision of the manuscript. R.P., M.M., M.E., M.S., M.D., G.U.H., M.B.: critical revision of the manuscript. S.J., N.F.: study concept and design, data analysis, drafting the manuscript

Competing interests: None

Data and materials availability: ADNI and A4 data are publicly available after registration on the study websites (ADNI: https://adni.loni.usc.edu/about/adni4/; A4: https://www.a4studydata.org). Subject-level connectivity of tau epicenters can be found in the supplementary.

hat gelöscht: awarded

Kommentiert [DN82]: Please make sure that all authors' contributions are accounted for, with every author's initials appearing at least once. If authors share initials, please use first initial and full surname. Where possible, please indicate which authors performed each experiment. Please provide author contributions in narrative form using sentences rather than list.

Kommentiert [DN83]: All consulting, whether paid or unpaid, and whether related to the present work or not, needs to be declared here. Any patents related to this work need to be stated here (cite patent title and filing #).

Kommentiert [I84R83]: Can this be generated from the COI forms? I do not have access to the forms of the individual authors, and each of them must have indicated this there

Kommentiert [DN85]: If materials will be shared with the scientific community via MTA, please provide a copy of the MTA to the editorial team. Please also indicate the point of contact for all MTA requests.

Kommentiert [I86R85]: Not applicable

hat gelöscht: and compliance with the respective studies' data use agreement

Table 1: Neuroimaging sample characteristics

ADNI (n=209)	CN Aβ- (n=69)	CN Aβ+ (n=68)	MCI Aβ+ (n=47)	Dementia Aβ+ (n=25)	p-value
Age	71.7±6.16[4]	73.6±6.22	74.4±6.12	75.8±8.02[1]	0.027
Sex (f/m)	38/31	46/22	21/26	7/18	0.004
MMSE	29.0±1.08[3,4]	29.1±1.30[3,4]	27.4±1.91[1,2,4]	23.4±3.49[1,2,3]	0.001
ADAS13 total	7.67±4.36[3,4]	8.25±4.73[3,4]	16.7±6.49[1,2,4]	27.8±8.63[1,2,3]	0.001
Centiloid	7.94±7.37[2,3,4]	64.3±35.3[1,4]	77.4±32.5[1,4]	96.0±30.1[1,2,3]	0.001
Amyloid tracer (FBB/FMM)	52/17	45/23	29/18	12/13	0.873
Tau-PET global SUVR	1.06±0.080[3,4]	1.09±0.077[3,4]	1.19±0.212[1,2,4]	1.35±0.399[1,2,3]	0.001
Tau-PET follow-up years	3.42±1.12[2,3,4]	2.80±1.21[1,3,4]	2.21±1.02[1,2]	1.68±0.60[1,2]	0.001
Number of tau-PET visits	2.39±0.65	2.68±0.74	2.66±0.67	2.40±0.50	0.034
Mean Framewise Displacement in resting-state fMRI	0.099±0.059	0.128±0.074	0.117±0.082	0.137±0.068	0.043
A4 (n=400)	CN Aβ- (n=55)	CN Aβ+ (n=345)			p-value
Age	70.0±4.15	72.2±4.91			<0.001
Sex (m/f)	28/27	150/195			0.377
Centiloid	11.1±7.82	69.5±31.4			<0.001
Global tau-PET SUVR	1.06±0.076	1.10±0.08			<0.001
MMSE	28.8±1.25	28.6±1.13			0.204
Mean Framewise Displacement in resting-state fMRI	0.106±0.067	0.110±0.066			0.666

Post-Hoc Tukey Test: [1]p<0.05 vs. CN Aβ-, [2]p<0.05 vs. CN Aβ+, [3]p<0.05 vs. MCI Aβ+, [4]p<0.05 vs. Dementia Aβ+. Means plus/minus standard deviations are displayed for continuous measures. Absolute numbers are displayed for categorical measures.

Figure legends:

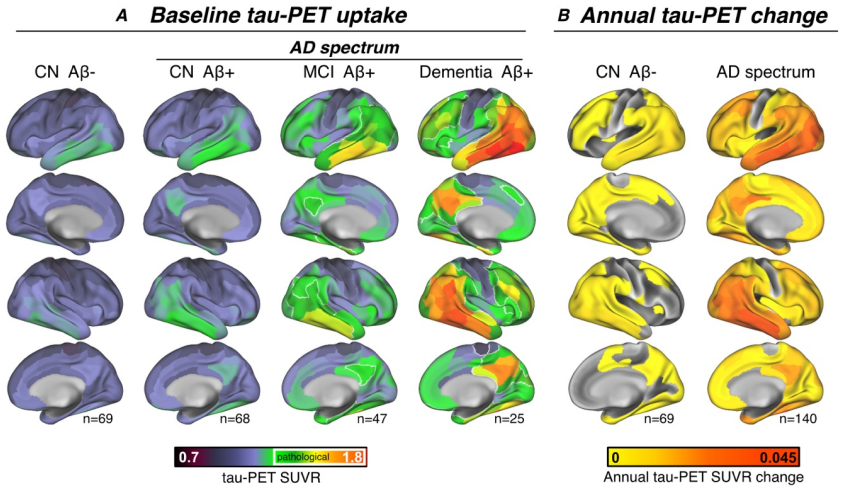


Figure 1: *(A) Baseline tau-PET SUVRs values stratified by diagnostic group and Aβ status, showing increasing tau load across the AD spectrum. SUVRs surpassing an abnormal cut-off of 1.3 are outlined in white. (B) Annual tau-PET SUVR change rates, as calculated using ROI-wise linear mixed models, stratified by amyloid status, illustrating faster tau accumulation in Aβ+ subjects, particularly in temporoparietal brain regions.*

hat gelöscht: *Table 2: Post-mortem sample characte* ... [4]

hat gelöscht: ----------Seitenumbruch----------

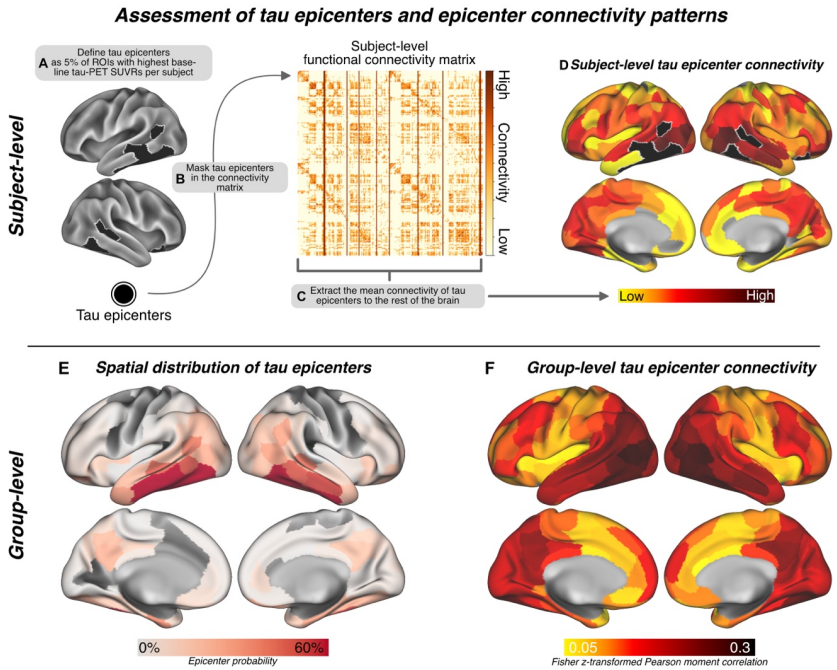


Figure 2: *(A) For each participant, 5% of brain regions with the highest baseline tau-PET SUVRs were defined as tau epicenters. (B) Epicenter masks were applied to (C) subject-specific connectivity matrices to (D) extract epicenter connectivity patterns. (E) Mapping of group-average epicenter probability and (F) epicenter connectivity.*

hat gelöscht: *level*

hat gelöscht: *level*

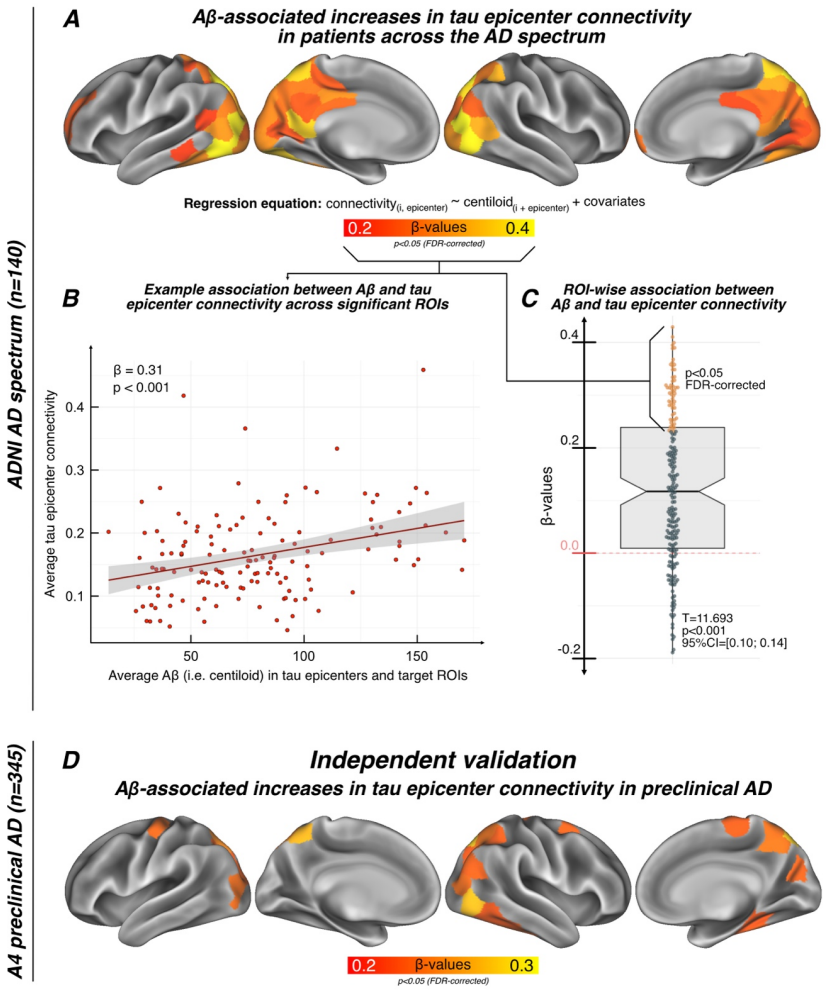


Figure 3: *(A) Association between Aβ and epicenter connectivity in ADNI. (B) Average association between Aβ and connectivity for significant ROIs (p<0.05, FDR-corrected) displayed in panel (A). (C) Unthresholded distribution of beta values displayed in panel (A) showing that beta-values are overall significantly larger than zero (p<0.001). (D) Validation of the association between Aβ and epicenter connectivity in A4. Regression-based associations were corrected for age, sex, ethnicity, scanner type, diagnosis and motion during the fMRI scan.*

Kommentiert [DN89]: Please use this word only to report statistical significance and always accompanied by a p value directly in the text, for example: (p=x.xx) or (p<x.xx). Any other uses of this word should be removed or replaced throughout the text.

Kommentiert [DN90]: Please use this word only to report statistical significance and always accompanied by a p value directly in the text, for example: (p=x.xx) or (p<x.xx). Any other uses of this word should be removed or replaced throughout the text.

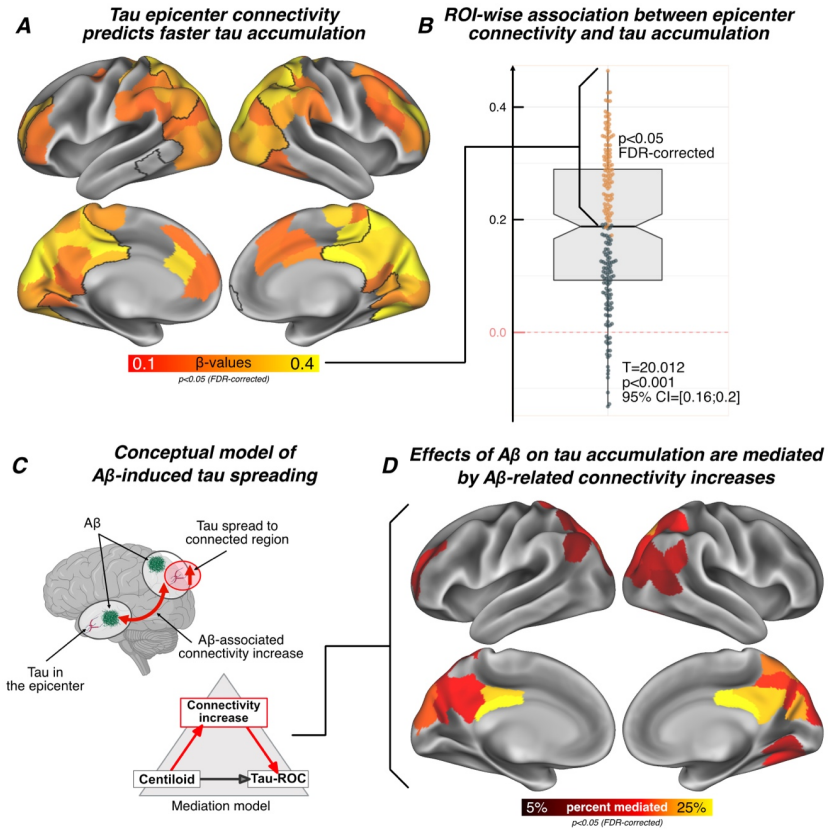


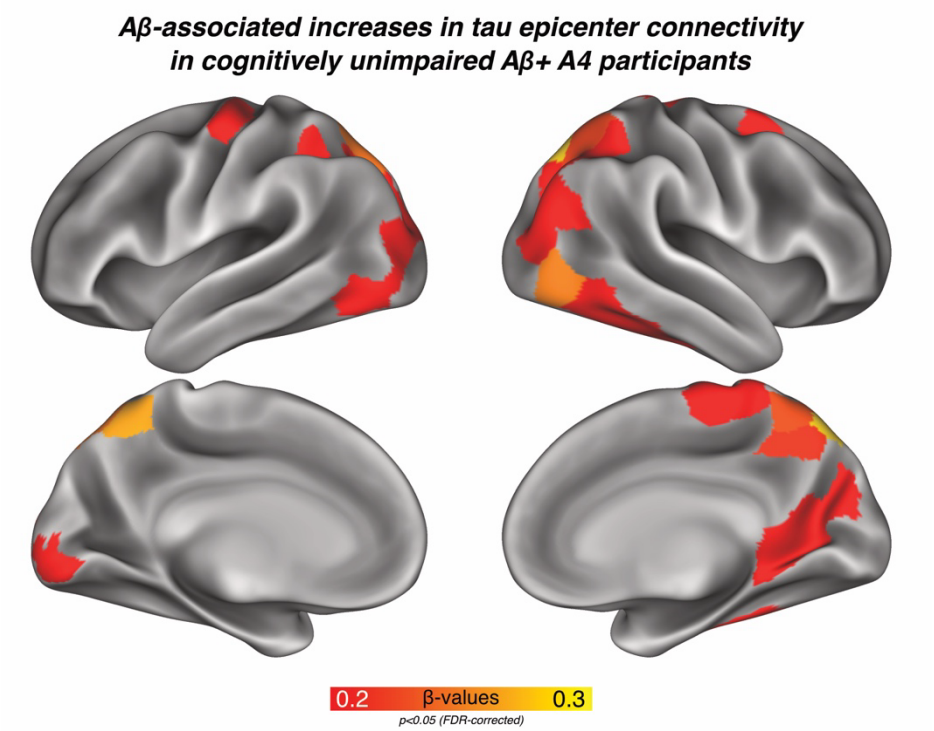
Figure 4: *(A) Association between stronger epicenter connectivity and faster tau accumulation in ADNI, including (B) the unthresholded distribution of beta-values, showing an overall positive association between epicenter connectivity and faster tau accumulation. (C) Conceptual model of Aβ-related tau spreading and (D) bootstrapped mediation showing that effects of Aβ on tau accumulation are mediated by increased epicenter connectivity. Regression-based associations and mediations were corrected for age, sex, ethnicity, scanner type, diagnosis and motion during the fMRI scan.*

hat gelöscht: Figure 4: *Post-mortem analyses of AD vs. control (CTRL) brains. (A) Overview of an example tissue staining. The red rectangle on the brain surface rendering highlights the anatomical location of the extracted probe in the primary visual cortex. The red rectangle on the microscopic image illustrates the location of the zoom-in images displayed in panel B. (B) Merged images of Dapi, NeuN, Aβ and c-Fos in an example control and AD subject. Group differences in (C) Aβ-plaque area, (D) neuron count (i.e. NeuN), and (E) the proportion of neurons with c-Fos positive signal.*¶ ... [5]

hat gelöscht: 5

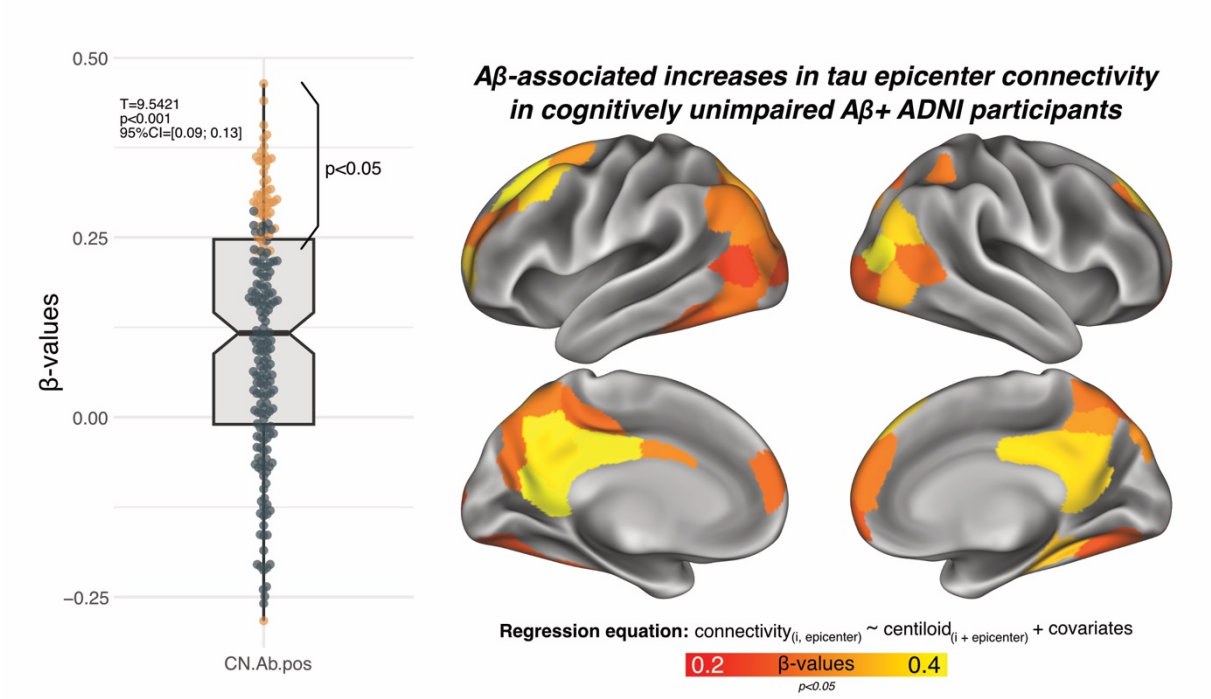
Seite 8: [1] hat gelöscht	**Nicolai Franzmeier**	**07.11.24 23:22:00**
Seite 14: [2] hat gelöscht	**Nicolai Franzmeier**	**08.11.24 09:49:00**
Seite 18: [3] hat gelöscht	**Nicolai Franzmeier**	**07.11.24 23:44:00**
Seite 33: [4] hat gelöscht	**Nicolai Franzmeier**	**08.11.24 10:33:00**
Seite 36: [5] hat gelöscht	**Nicolai Franzmeier**	**08.11.24 09:40:00**

Supplementary Figures
Fig. S1:



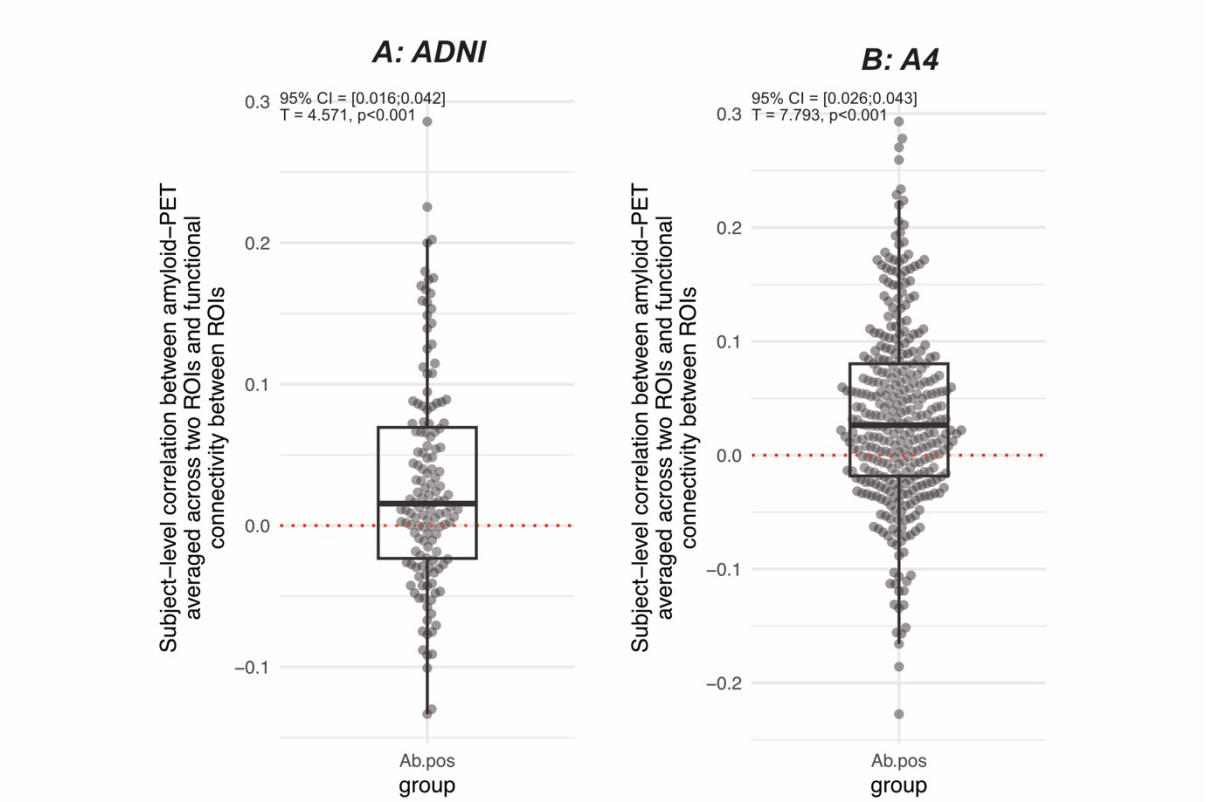
Exploratory sub-analysis showing the association between Aβ and epicenter connectivity in cognitively unimpaired Aβ+ subjects of the A4 cohort, reclassified as Aβ+ at a global amyloid-PET SUVR threshold of 1.15 (n=322) as recommended by the A4 imaging core. The surface rendering shows the spatial pattern of significant (p<0.05, FDR-corrected) associations between amyloid-PET levels in the tau epicenter and target ROI and the connectivity between the epicenter and the target ROI.

Fig. S2:



Exploratory sub-analysis showing the association between Aβ and epicenter connectivity in cognitively unimpaired Aβ+ subjects of the ADNI cohort (n=68). The surface rendering shows the spatial pattern of significant (p<0.05) associations between amyloid-PET levels in the tau epicenter and target ROI and the connectivity between the epicenter and the target ROI. The beeswarm plot shows that the overall distribution of beta values is significantly greater than zero as shown by a one sample t-test, with 95% Confidence intervals not overlapping with zero. Yellow dots in the beeswarm plot reflect significant ROIs projected on the brain surface.

Fig. S3:



Beeswarm plots, illustrating the distribution of subject-level correlation coefficients between amyloid-PET summarized across any given ROI pair and subject-level functional connectivity matrices for Aβ+ subjects of ADNI and A4. Results show an overall positive distribution of correlation coefficients as indicated by a significant t-test against zero, and 95% confidence intervals of the distributions not including zero. These data suggest that ROI pairs with a combined high amyloid load tend to have higher functional connectivity within individuals.