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Amidst an amygdala renaissance in Alzheimer's disease

Kaitlin M. Stouffer,[1,2,3] Xenia Grande,[4,5] Emrah Düzel,[4,5] Maurits Johansson,[6,7,8] Byron Creese,[9,10] Menno P. Witter,[11,12] Michael I. Miller,[1,2,3] Laura E. M. Wisse[13,†] and David Berron[4,6†]

[†]These authors contributed equally to this work.

The amygdala was highlighted as an early site for neurofibrillary tau tangle pathology in Alzheimer's disease in the seminal 1991 article by Braak and Braak. This knowledge has, however, only received traction recently with advances in imaging and image analysis techniques. Here, we provide a cross-disciplinary overview of pathology and neuroimaging studies on the amygdala.

These studies provide strong support for an early role of the amygdala in Alzheimer's disease and the utility of imaging biomarkers of the amygdala in detecting early changes and predicting decline in cognitive functions and neuropsychiatric symptoms in early stages. We summarize the animal literature on connectivity of the amygdala, demonstrating that amygdala nuclei that show the earliest and strongest accumulation of neurofibrillary tangle pathology are those that are connected to brain regions that also show early neurofibrillary tangle accumulation. Additionally, we propose an alternative pathway of neurofibrillary tangle spreading within the medial temporal lobe between the amygdala and the anterior hippocampus. The proposed existence of this pathway is strengthened by novel experimental data on human functional connectivity.

Finally, we summarize the functional roles of the amygdala, highlighting the correspondence between neurofibrillary tangle accumulation and symptomatic profiles in Alzheimer's disease. In summary, these findings provide a new impetus for studying the amygdala in Alzheimer's disease and a unique perspective to guide further study on neurofibrillary tangle spreading and the occurrence of neuropsychiatric symptoms in Alzheimer's disease.

1 Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, 21218, USA
2 Kavli Neuroscience Discovery Institute, Johns Hopkins University, Baltimore, MD, 21218, USA
3 Center for Imaging Science, Johns Hopkins University, Baltimore, MD, 21218, USA
4 German Center for Neurodegenerative Diseases (DZNE), 39120, Magdeburg, Germany
5 Institute for Cognitive Neurology and Dementia Research, Otto-von-Guericke University, 39106, Magdeburg, Germany
6 Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, 205 02, Lund, Sweden
7 Division of Clinical Sciences, Helsingborg, Department of Clinical Sciences Lund, Lund University, 221 84, Lund, Sweden
8 Department of Psychiatry, Helsingborg Hospital, 252 23, Helsingborg, Sweden
9 Department of Clinical and Biomedical Sciences, Faculty of Health and Life Sciences, University of Exeter, EX4 4PY, Exeter, UK
10 Division of Psychology, Department of Life Sciences, Brunel University London, UB8 3PH, Uxbridge, UK
11 Kavli Institute for Systems Neuroscience, NTNU Norwegian University of Science and Technology, 7491, Trondheim, Norway

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12 KG. Jebsen Centre for Alzheimer's Disease, NTNU Norwegian University of Science and Technology, 7491, Trondheim, Norway
13 Diagnostic Radiology, Department of Clinical Sciences Lund, Lund University, 211 84, Lund, Sweden

Correspondence to: Kaitlin Stouffer
307D Clark Hall, Johns Hopkins University, 3400 N Charles St, Baltimore, MD, 21218, USA
E-mail: kstouff4@jhmi.edu

Correspondence may also be addressed to: David Berron
German Center for Neurodegenerative Diseases (DZNE), Leipziger Straße 44, 39120 Magdeburg, Germany
E-mail: david.berron@dzne.de

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Introduction

Alzheimer's disease is one of the most heavily studied areas in neurological and biomedical research today. However, despite the growing breadth of Alzheimer's disease research across institutions and fields, the span of brain areas typically investigated, particularly in relation to neurofibrillary tangle (NFT) pathology, has remained quite narrow. As emphasized by Braak and Braak in the early 1990s,[1] the transentorhinal region (TER), entorhinal cortex (ERC) and hippocampus [including subiculum and cornu ammonis 1 (CA1)] are among the first areas known to be affected by NFT pathology. Consequently, both imaging and histopathological studies over the last three decades have focused on these regions not only with respect to classical neuropathological staging guidelines,[2,3] but also in studies attempting to identify early biomarkers of Alzheimer's disease[4,5] and pathophysiological mechanisms of causation.[6] Advancements in imaging technologies over the past decade,[7-10] however, have enabled the capture of more varied biological data (e.g. molecular images) across wider spatial windows, consequently facilitating a broader scope of investigation. Evidence from a number of recent imaging studies has particularly begun to suggest that the amygdala (Fig. 1A) might play a role complementary to the TER, ERC, and hippocampus in early Alzheimer's disease.

Here, we first review these recent imaging studies in the context of earlier work predating and following Braak and Braak's historic observations[1] to illustrate the mounting evidence of the amygdala's role in Alzheimer's disease. While not precluding the amygdala's importance as a reservoir of amyloid-β (Aβ) pathology, we focus here on the proposed role of the amygdala in NFT pathology as NFT pathology has been most closely associated with neurodegeneration and cognitive decline.[11-14] (While some studies also focus on neuropil threads, for simplicity we will refer to tau pathology in Alzheimer's disease as NFT pathology.) Beginning with the late 1970s and early 1980s, we survey some of the findings through the turn of the century in the area of post-mortem histopathological analysis that implicate the amygdala in Alzheimer's disease NFT pathology. We note the relative dearth of literature on the amygdala in Alzheimer's disease in the late 1990s and early 2000s and consequently discuss some of the possible reasons why the amygdala underwent less investigation than the TER, ERC and hippocampus during this time. Finally, we highlight the evidence that has emerged, predominantly as a consequence of novel imaging technologies and analytical techniques, that is rekindling interest in the amygdala and supporting its role in Alzheimer's disease NFT pathology.

In the second half of the article, we offer further perspective on this role by linking the findings surveyed in the first half both to connectivity studies and symptomatology in Alzheimer's disease. In particular, we interpret the early sites of NFT accumulation in the amygdala in light of its connectivity profile obtained from the animal literature. We subsequently suggest a role for the amygdala as part of an alternative pathway of NFT spreading in the medial temporal lobe (MTL), apart from that classically described between regions of the ERC and hippocampus. We support the existence of such a pathway here, with novel human data. We also discuss the link between NFT accumulation in the amygdala and specific (neuropsychiatric) symptomatology in Alzheimer's disease, in light of the functional associations of the amygdala and its networks.

In summary, with these novel findings and resurfacing neuropathological observations, as well as the patterns of connectivity and clinical manifestations associated with the amygdala, we suggest that the amygdala should play a more central role in Alzheimer's disease and particularly NFT-related, research in the future. As its role in the symptomatology in Alzheimer's disease and the spreading of NFT pathology continues to become evident, we expect imaging measures of the amygdala to be useful biomarkers for clinical trials and ultimately clinical practice.

Historical trajectory of the amygdala in Alzheimer's disease research

Early evidence of the importance of the amygdala in Alzheimer's disease

The earliest evidence of NFT pathology in the amygdala in the context of Alzheimer's disease dates back to the 1970s and 1980s, in a collection of post-mortem analyses, similar to that presented by the Braaks. Though often underemphasized, the Braaks, themselves, indicated the appearance of NFTs in the amygdala as early as stage II, growing to moderate amounts seen in stages IV and V.[1] Their report followed a boom time in the 1970s and 1980s when numerous post-mortem studies highlighted the presence of NFTs in the amygdala in Alzheimer's disease.[15-22] While the number of cases included in these reports was modest (between 10 and 48), the findings point unanimously towards the importance of the amygdala as an accumulation site for NFTs in Alzheimer's

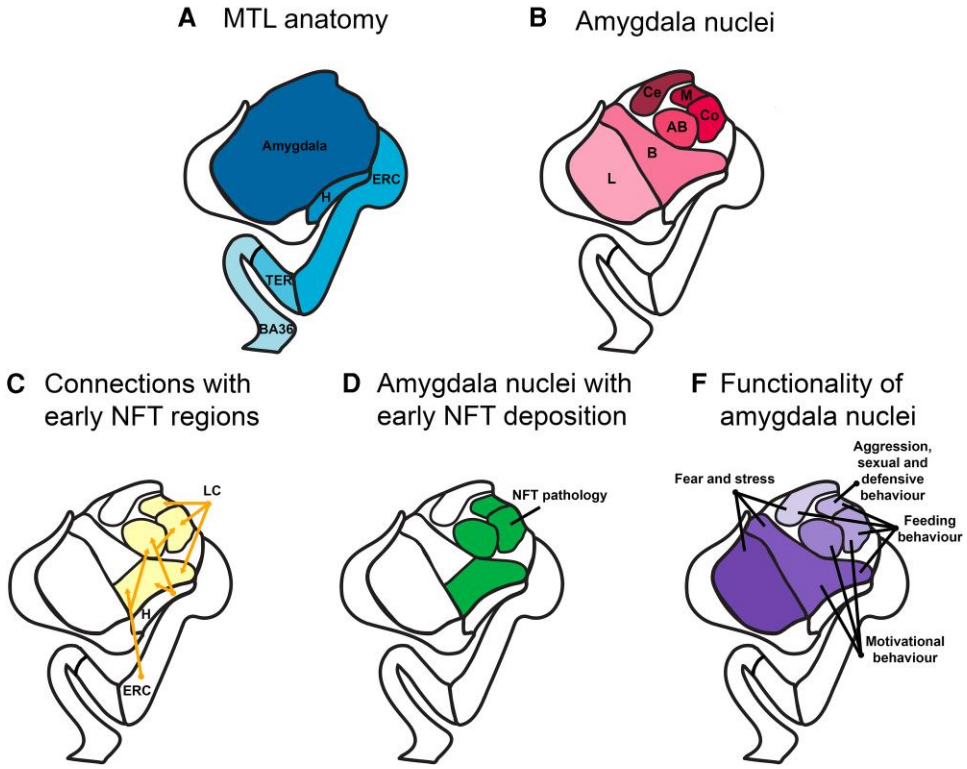

Figure 1 An overview of structural, connectional and functional aspects of the amygdala. (**A**) Position of the amygdala in the anterior medial temporal lobe (MTL). (**B**) Different nuclei in the amygdala. (**C**) Connections of the amygdala with other early NFT regions: the entorhinal cortex, the hippocampus and the locus coeruleus. (**D**) Preferential localization of NFT accumulation within the amygdala. (**E**) Different functions associated with amygdala nuclei. AB = accessory basal nucleus; B = basal nucleus; BA = Brodmann area; Ce = central nucleus; Co = cortical nuclei; ERC = entorhinal cortex; H = hippocampus; L = lateral nucleus; LC = locus coeruleus; M = medial nucleus; NFT = neurofibrillary tangles; TER = transentorhinal region. Note that different nomenclatures and groupings exist for the nuclei of the amygdala, where the following names can be used more or less synonymously: basal nucleus = basolateral nucleus; accessory basal nucleus = basomedial nucleus.

disease. A mixture of early onset versus late onset Alzheimer's disease cases were included in the different studies, and while most cases received a diagnosis of dementia before death, cases in earlier clinical stages were also included. Regardless of the composition of the study population, the amygdala was a clear site for NFT accumulation in all studies, indicating the importance of the amygdala throughout the different clinical stages of Alzheimer's disease. Interestingly, neuron loss, often thought to be the result of NFT pathology,[12,14] was also reported in the amygdala in dementia cases with Alzheimer's disease neuropathologic change.[19,23]

Diminished focus in Alzheimer's disease-related research on the amygdala due to methodological challenges

Despite these early findings highlighting the involvement of the amygdala in NFT pathology, the late 1990s and early 2000s experienced a relative dearth in interest around the amygdala and consequently in findings. One potential cause of this diminished focus was the desire to focus on earliest (stage I) NFT pathology, both for diagnostic purposes and to uncover the yet unknown pathophysiological mechanisms of Alzheimer's disease. Hence, despite the Braaks' observation of NFT pathology in the amygdala in stage II,[1] emphasis was often placed instead on their observations of NFT pathology in the hippocampus, ERC and TER, as areas of earliest pathology. A second potential cause might rest in the relative difficulty of measuring the amygdala in imaging studies, which were beginning to emerge during this time. The amygdala has historically proven a more difficult structure to segment, compared with the ERC and hippocampus,[24] and as a result, has made it less conducive to manual and automatic identification and downstream analysis. Finally, the focus on Alzheimer's disease's hallmark clinical symptom of 'episodic memory loss' supports a third potential cause of omission, with the hippocampus carrying functional focus in Alzheimer's disease and the amygdala, instead, being associated with neuropsychiatric symptoms and thus linked more to primary psychiatric conditions such as affective disorders and schizophrenia.[25-27] Interestingly, however, it is now recognized that neuropsychiatric symptoms are an early symptom and potentially even the earliest in some individuals, of Alzheimer's disease.[28] We discuss the role of the amygdala in the context of these occurring neuropsychiatric symptoms further in the last section.

Emerging evidence in support of an early role for the amygdala in Alzheimer's disease

Evidence has begun to emerge over the past 510 years that suggests the amygdala can be repositioned as a key area for study in relation to Alzheimer's disease. Imaging technologies and analytical techniques have begun to offer scientists wider windows into neuroanatomy, facilitating the emergence of findings outside the immediate focus regions of past technologies. Concurrently, technologies are

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developing to match this spatial breadth with information depth, with both the variety and resolution of measures increasing at a rapid rate. This has facilitated the study of pathological measures, such as patterns of NFTs, in a larger spatial context of surrounding tissue (e.g. in 3D), and the measurement of shape changes (e.g. local volume changes) on MRI in particular structures with more accuracy. Together, these technologies have enabled different groups to study Alzheimer's disease from new visual and phenomenological angles, which have independently highlighted an important role for the amygdala in Alzheimer's disease.

Post-mortem histological 3D reconstruction of NFT pathology in the amygdala

One class of evidence that implicates the amygdala particularly in Alzheimer's disease NFT pathology stems from newly arising techniques to build state-of-the-art datasets with reconstructed histopathological measures in the space of 3D MRI, as demonstrated both by Yushkevich *et al.*[29] and Stouffer *et al.*[30] Such datasets offer the opportunity for investigating with both high resolution and broad spatial coverage the distributions of pathology in individual subjects. Both groups report high levels of NFT pathology not only in expected areas, such as the TER and ERC, but also in the amygdala, in cases with early[29] and advanced[31] Alzheimer's disease pathology. Furthermore, these 3D reconstructions of digital pathology have afforded high enough resolution for both groups to observe NFT pathology aggregating particularly within the inferior-medial domain of the amygdala (Fig. 1B; note that given the disagreement on the parcellation and nomenclature of the amygdala nuclei, we chose the word 'domain' to refer broadly to the different regions within the amygdala, particularly in reference to localizing NFT accumulation). This spatial segregation they both report matches the general trend from previous post-mortem studies that compared the location of NFT pathology in specific amygdala nuclei in a 2D manner, often in single or a few slices,[15-19,21,22] but note that one study indicated a different pattern of NFT accumulation in the amygdala.[1]

Tau-PET imaging highlights the amygdala as a key region for NFT accumulation

A second line of evidence amassing in support of the amygdala's role in Alzheimer's disease pathology harnesses the techniques of molecular imaging, such as tau-PET, to interrogate pathological distributions *in vivo*. Berron *et al.*[32] used an event-based modelling (EBM) approach coupled with tau-PET imaging in cognitively unimpaired individuals and patients with mild cognitive impairment (MCI), both Aβ positive, to identify the sequence of brain regions affected by NFT pathology. While the amygdala was not included in the development of the EBM sequence, their results show strong tau-PET signal in the amygdala in the earliest EBM stages (note that staging using tau-PET is not synonymous to Braak staging; Fig. 2). The results of Yoon *et al.*[33] echo these findings with highest burden of NFT pathology found in the amygdala in a group of Aβ-positive subjects with and without cognitive impairment, with both types of pathology characterized through PET imaging.

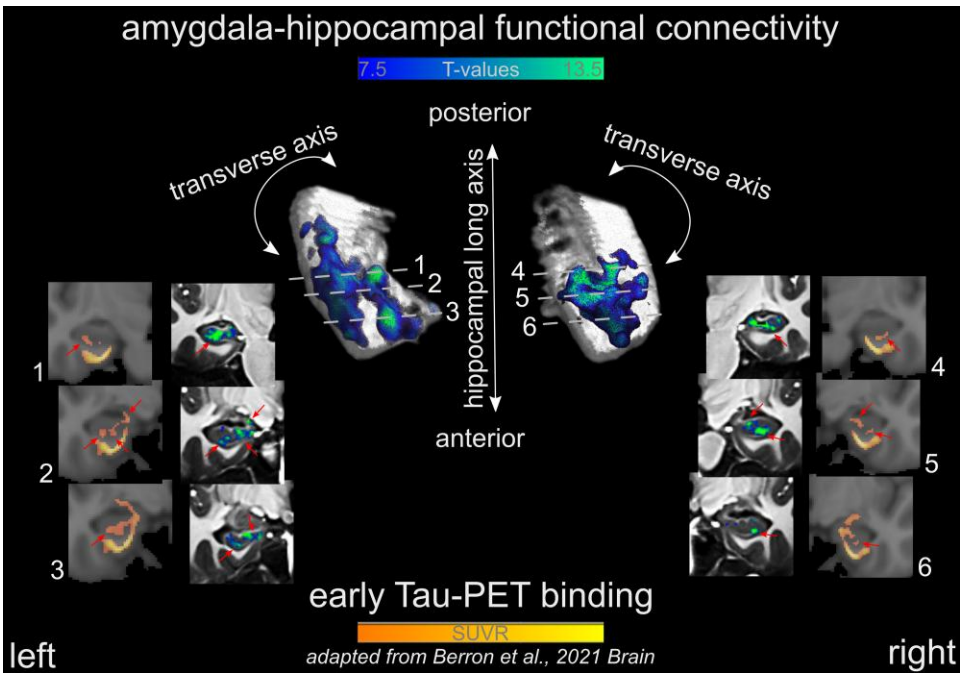

Figure 2 Functional connectivity between the amygdala and hippocampus. Displayed in blue/green are the significant (FWE $P < 0.05$) clusters of a seed-to-voxel functional connectivity analysis in young individuals between the amygdala and hippocampal voxels for each hemisphere, respectively. The clusters are obtained by a one-sample *T*-test over all participants' connectivity estimates. These estimates resulted from correlating residual time series between the amygdala (seed) and hippocampal voxels on the participant level (non-directional functional connectivity). Significant clusters are projected onto a 3D hippocampal mask (*middle* grey figures). Outer slices display the clusters at the location of the stippled line in coronal view (1–6). The blue/green colour scheme indicates the height of T-values within significant clusters (significant with FWE $P < 0.05$ from $T > 7.4$). Note that results for the left and right hemispheres have been obtained by separate analyses. More details and results can be found in the Supplementary material, section 1. For comparison, tau-PET signal in medial temporal lobe (MTL) subregions from a recent study in patients with early Alzheimer's disease from the Swedish BioFINDER study[32] are shown on representative slices side-by-side to the functional connectivity results. The orange/yellow colour scheme indicates the standardized uptake value ratio (SUVR) values within significant clusters. FWE = family-wise error.

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Similar results were found in two other cohorts with highest, or among the highest, tau-PET signal in the amygdala in Aβ-positive cognitively unimpaired individuals,[34,35] suggesting an early role for the amygdala even before cognitive symptoms are observed. In addition, Insel and colleagues[36] used disease time as a measure of disease severity to identify brain regions with the highest tau-PET uptake. Again, the amygdala was the earliest brain region showing the highest mean tau-PET uptake as early as 10 years before an Alzheimer's disease diagnosis and even preceding the appearance of NFT pathology in the ERC. Finally, Leuzy and colleagues[37] used longitudinal tau-PET to identify brain regions with the largest annual increase in tau-PET uptake. Combining an EBM and a clustering approach, they sought to characterize the combination of brain regions amidst 35 regions of interest that showed the largest annual increase in tau-PET uptake. For Aβ-positive cognitively unimpaired individuals, the regions showing this largest increase were the ERC, the hippocampus and the amygdala.

Hence, the appearance of NFT pathology in the amygdala via molecular imaging echoes the distributions found post-mortem via traditional histopathological staining and consequent mapping to 3D. Indeed, the correspondence between patterns observed through histopathological studies and molecular imaging has also motivated efforts to use tau-PET as a means of approximating Braak stages of individuals *in vivo*, where measurable NFT pathology in the amygdala has been cited, for instance, in as early as stage III.[38] While post-mortem studies still achieve higher resolutions in reported distributions of NFT pathology and sensitivity to the earliest stages, the increasing availability of tau-PET as well as its use *in vivo* have enabled the study of larger and more diverse cohorts. As manifested in the findings reported here, this, in turn, has enabled both spatial and longitudinal studies of NFT pathology, which further elucidate the amygdala as not just being affected by NFT pathology, but being specifically affected by NFT pathology in early (preclinical and prodromal) stages of Alzheimer's disease. This suggests that imaging measures of the amygdala could be an attractive biomarker, for example, for enrichment in clinical trials or for monitoring disease progression.

Amygdala atrophy on structural MRI relates to downstream cognitive impairments and neuropsychiatric symptoms

A final class of growing evidence on the amygdala's role in Alzheimer's disease is that from structural MRI analysis. While MRI has the advantage of studying cohorts *in vivo*, most of this evidence stems from studies that classified individuals according to clinical diagnoses of Alzheimer's disease rather than those determined by the presence of Aβ pathology according to PET or biofluid measures. As such, amygdala observations associated with these studies have not typically been linked directly to biological Alzheimer's disease and characteristic patterns of NFT pathology. Rather, such changes have been associated with clinical changes associated with Alzheimer's disease, such as cognitive and neuropsychiatric symptoms.

For instance, several studies showed volumetric MRI measures of the whole amygdala to correlate directly with measures of memory performance or global cognition.[39-42] In other studies, amygdala volume was either the sole or an independent predictor of performance on cognitive tests when other MTL structural measures were also included in the model.[43-45] Additionally, right amygdala volume, beyond other structural brain measures, was associated with the worsening of neuropsychiatric symptoms, such as agitation and aggression, in patients with cognitive impairment.[45] Finally, Liu *et al.*[46] found that amygdala volume was a predictor of conversion to dementia.

Another body of evidence in structural MRI has focused not only on measurements of global amygdala volume but also local shape changes in the amygdala and their link to Alzheimer's disease. Recent work from Stouffer *et al.*[31] coupled manual amygdala segmentations of longitudinal MRI scans with diffeomorphometry to achieve estimates of atrophy rate per subject and across populations, addressing some of the challenges that have hindered study of the amygdala previously (e.g. automatic segmentation schemes and variability in image sequences over time). They showed significantly higher rates of global amygdala volume loss in subjects converting to MCI or to dementia of the Alzheimer's type (clinical diagnosis without biomarker confirmation) (6.8% and 11.6% volume loss/year, respectively) than in stable controls (1.5% volume loss/year). Furthermore, they localized areas of greatest volume loss on average across subjects in each cohort to the inferior-medial domain of the amygdala with least loss observed laterally. Similarly, Miller *et al.*[47] used diffeomorphometry to characterize finer-grained atrophy, measured at the level of vertex-wise expansion or contraction in surface meshes of the amygdala, generated from segmentations from MRI scans of controls versus patients with clinical dementia of the Alzheimer's type. Interestingly, they too reported most significant atrophy in the inferior-medial domain, encompassing the areas of densest NFT accumulation in post-mortem reconstructions,[29,31] with extensions laterally[47] possibly due to NFT pathology having spread laterally in the clinical stage of dementia or to other comorbid pathologies. Finally, a recent study used spherical mapping also to characterize vertex-wise differences in amygdala shape measured across a population with post-mortem MRI. They highlighted significant 'inward deformation' (atrophy) both in the inferior-medial domain with extensions laterally in individuals with Alzheimer's disease-specific pathology,[48] providing initial evidence for Alzheimer's disease-specific localized atrophy in the amygdala. However, this study was limited by linkage to semi-quantitative measures of Alzheimer's disease pathology that represented the global burden in the hemisphere rather than a local burden in the amygdala.

Finally, echoing the EBM approach in the tau-PET studies described above, a last line of evidence in structural MRI involves the use of longitudinal MRI scans coupled with changepoint temporal modelling to estimate not just where but when atrophy occurs in various areas of the MTL during the course of individuals' progression from normal cognition to MCI and clinical dementia of the Alzheimer's type. For instance, Miller *et al.*[49] couple diffeomorphometry with changepoint modelling in analysing longitudinal MRI scans from individuals along this progression. They report most significant atrophy globally within the ERC, followed by the amygdala and then the hippocampus when comparing both diseased populations to controls. Furthermore, they estimate the ERC to be the structure with the earliest onset of atrophy, followed by the amygdala, and then the hippocampus, highlighting amygdala atrophy as an early event in the progression to MCI and ultimately clinical dementia of the Alzheimer's type.

Hence, in general, structural MRI has facilitated investigation and consequent manifestation of changes in global amygdala volume and more local shape characteristics (e.g. regional surface area contraction) that have been linked to the earliest stages of cognitive decline, with a large portion of subjects progressing onto clinical dementia of the Alzheimer's type. Together, this body of

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evidence suggests, as in the previous studies, that the amygdala may play a role not just in Alzheimer's disease, generally, but particularly in its earliest stages, amidst the onset of cognitive and neuropsychiatric symptoms. Consequently, the continued study of the amygdala through modes of clinical imaging, such as MRI before and during the disease course, will be integral both to understanding and ultimately monitoring and even predicting patients' progressing Alzheimer's disease symptomatology.

Anatomical evidence for amygdala-associated tau spread in Alzheimer's disease

The sequential emergence of NFT pathology across interconnected brain networks has led to the hypothesis that NFT pathology spreads along strongly connected brain regions through a connectional transmission mechanism.[50] There is a wealth of *in vivo* human studies using functional MRI (fMRI) that lend support to this (summarized in Vogel *et al.*[51]). Studies found that NFT pathology accumulates preferentially in regions that are closely connected to epicentres—regions that show high levels of brain alterations in early disease stages.[52-54] Longitudinal imaging studies further showed that regions that are closely connected to those epicentres show the fastest rate of NFT accumulation.[55,56] Finally, studies using subtype- or individual-specific epicentres showed even improved predictive power, suggesting considerable epicentre variability between individuals.[55,57] However, the spreading of NFT pathology within the MTL, and in particular the role of the amygdala herein, has received less attention. Hence, we review here key aspects of the amygdala's and MTL's connectivity obtained from animal literature. We complement these findings by presenting novel *in vivo* experimental data in humans using high-field fMRI. Not only do these biological attributes further support the body of evidence presented above, but taken together, they even suggest that the amygdala might play a unique role in NFT spreading in the MTL in early Alzheimer's disease stages.

Amygdala connectivity from animal studies highlights integral connections with early NFT regions

Early NFT pathology in the amygdala is not surprising when considering the connectivity pattern of the amygdala. The animal literature shows that the amygdala has strong connections with other brain regions that show very early NFT accumulation,[1] including the locus coeruleus, the perirhinal and entorhinal cortices (which include the TER), and the region of the subiculum that borders with the CA1 of the hippocampus, also referred to as the prosubiculum[58-61] (Fig. 1C). Interestingly, the connections between the amygdala and the hippocampus, as documented in animals, are reciprocal and preferentially connect the anterior domain of the hippocampus with the inferior-medial domain of the amygdala[58,59,61] (Fig. 3). This inferior-medial domain, as discussed above, was the region found to show the densest NFT accumulation in 3D reconstruction studies[29,31] and older histopathological studies[15-19,21,22] (Fig. 1D), as well as show significant atrophy in longitudinal MRI studies.[31,47] Strikingly, the reciprocal connections with the anterolateral part of the ERC are also associated with this inferior-medial amygdala domain.[58,60,64]

Importantly, tracing studies in a variety of animal species have shown different amygdala nuclei to have very different connections and, particularly relevant for the present article, that the overall structure and organization is evolutionarily relatively preserved across these species.[65] This suggests that these connectivity patterns can be taken to hold true in humans as well. In general, this connectivity pattern of the amygdala further explains early occurrence of NFT pathology in not just the amygdala as a whole structure, but particularly the inferior-medial domain.

Animal and human studies of amygdala connectivity highlight connections for tau spread to anterior hippocampus

The connectivity of the amygdala also seems to have implications for the occurrence of NFT pathology in other MTL regions and might provide a different pathway of NFT spreading to the anterior hippocampus. The anterolateral ERC and the adjacent TER have traditionally been implicated as an early locus of NFT pathology.[1] (Although TER as such has never been formally described in animals, it has been proposed that it represents a part of perirhinal Brodmann area 35 that directly borders ERC laterally.[62,63] For the purpose of the following connectional summary, we opt to include it into ERC.) NFT pathology in Alzheimer's disease is also observed in hippocampal subregions CA1 and subiculum early on.[1] Within the hippocampus, both the anterior and extreme posterior regions seem to harbour the same level of NFT pathology, with a paucity of pathology in the middle region of the hippocampus (body). This distribution of pathology appears in early stages,[29] but has also been observed to be maintained even in advanced stages of Alzheimer's disease.[30,31] Interestingly, the anterolateral ERC has preferential reciprocal connections to posterior rather than anterior parts of the hippocampus.[66-68] Assuming a model of NFT spread through connected brain regions, the occurrence of NFT pathology in the posterior hippocampus can be explained by early NFT pathology in the anterolateral ERC through these preferential reciprocal connections. However, the appearance of early NFT pathology in the anterior hippocampus still lacks a plausible trajectory, particularly in conjunction with early NFT pathology in the ERC. As discussed above, the amygdala does have strong reciprocal connections with the anterior hippocampus.[58,59,61] Therefore, the amygdala could be hypothesized to be an additional pathway for NFT spread within the MTL and potentially explain this occurrence of early pathology in the anterior hippocampal region. See Fig. 3 for an illustration of amygdala connectivity and early accumulation sites of NFT pathology.

In humans, the amygdala-hippocampal functional connectivity resembles the described connectivity profile derived from animal studies. A functional connectivity analysis on ultra-high field 7 T MRI data (see Grande *et al.*[69] and Supplementary material, section 1 for methods and results) revealed main functional connectivity between the amygdala and an area in the anterior hippocampus at the level where the uncal apex separates from the rest of the hippocampus (Fig. 2). That area extends towards dentate gyrus and CA3 but clearly covers subiculum and CA1. Thus, human high-resolution functional connectivity data are in line with connectivity data from the animal literature and confirm connectivity primarily between the amygdala and the anterior hippocampal domain, with a focus on the border domain between CA1 and subiculum (prosubiculum). Strikingly, these connectivity patterns overlap with the areas of earliest accumulation of NFT pathology in the hippocampus of individuals without dementia, seen primarily in the anterior domain, as outlined in Fig. 2 (adapted from Berron *et al.*[32]). Taken

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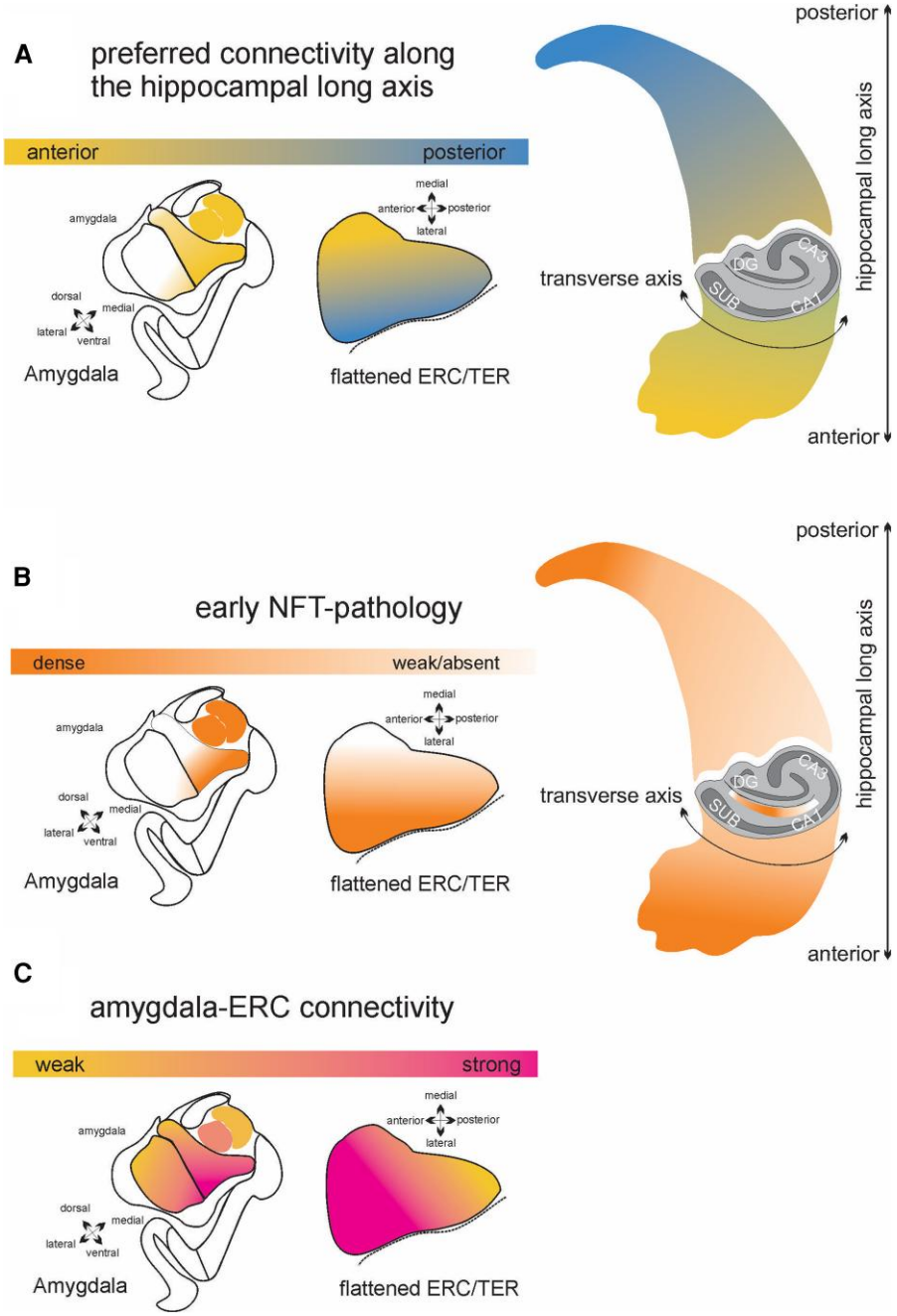

Figure 3 Schematic summary of preferred connectional relationships between amygdala, entorhinal cortex and hippocampus consistently established in animal studies and the density of early NFT pathology in patients with Alzheimer's disease. (**A**) *Right*: Schematic representation of the hippocampus indicating the longitudinal axis from anterior (yellow) to posterior (cyan). *Middle*: The same colour code indicates the preferred connectivity of the entorhinal cortex (ERC) along the hippocampal long axis. *Left*: The same colour code indicates the preferred connectivity of the amygdala along the hippocampal long axis. (**B**) Schematic representation of preferred distribution of early stage NFT pathology in the amygdala, ERC and hippocampal CA1/subiculum. The amygdala shows early NFT pathology in the inferior-medial domain (*left*), in the ERC early NFT pathology is mainly seen in anterolateral parts (*middle*), whereas in hippocampus (*left*) both anterior and posterior parts are indicated with a preferred density on both extents. Additionally, a density gradient along the transverse axis with high density in the border region between CA1 and subiculum has been indicated. (**C**) Schematic representation of density gradients in reciprocal connectivity between amygdala and ERC. The densest connections are between the inferior part of the lateral and basolateral nucleus, with the anterior-lateral portion of ERC (magenta). The dashed line in the flattened representation of ERC/TER represents the fundus of the collateral and rhinal sulcus. Note, in the flattened representation of ERC, we included TER. TER, originally defined as a transition area between ERC and the perirhinal cortex area 36, likely overlaps with part of the perirhinal cortex area 35.[62,63] Regarding its hippocampal connectivity, projections of area 35 in animals are largely limited to the proximal subiculum and weakly to the adjacent distal CA1 at the posterior levels of the hippocampus, i.e. similar to projections from the lateral ERC. CA = cornu ammonis; NFT = neurofibrillary tangles; TER = transentorhinal region.

together, these results further support the hypothesis of NFT pathology spreading via an amygdala-anterior hippocampal route in addition to that traditionally described between the ERC and posterior hippocampus.

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The amygdala as an additional pathway of NFT spreading: discussion and future research

Following a model of NFT spread via neuronal connections, the previous section introduced the hypothesis of an amygdala-anterior hippocampal pathway of NFT pathology spread as a potential explanation of the early appearance of NFT pathology in the anterior hippocampus. Nevertheless, open questions remain around the exact timing and initial sourcing of NFT pathology with respect to its appearance in the amygdala, hippocampus and ERC. As such, there exist alternative hypotheses and variations on the one presented above, in which the amygdala is likely posed as a source of NFT pathology that subsequently spreads to the anterior hippocampus. For instance, one important question is where the NFT pathology in the amygdala is coming from; i.e. whether it starts in the amygdala or comes from other early NFT regions, such as the anterolateral ERC. While the answer does not affect the feasibility of NFT spread from the amygdala to the anterior hippocampus, the question nevertheless serves as a starting point for future research also to understand the complementary roles the amygdala and ERC might play in spreading of NFT pathology. Additionally, the reciprocal connections between the amygdala and anterior hippocampus do not provide evidence for the directionality of potential NFT spread between these two structures. Besides the amygdala, the anterior hippocampus could also serve as a starting point of NFT pathology and thus initiate spread from the anterior hippocampus to the amygdala. It would be unclear in this scenario where the NFT pathology in the anterior hippocampus would come from; however, it is possible that the anterior hippocampus is another starting point for NFT pathology in the MTL, besides the ERC-TER border region. One argument in favour of this is the report of a few isolated tangles in CA1 in stage I, with those in the amygdala only reported in stage II.[1] It is unclear, though, how much weight can be placed on these descriptions as they were based on only a few histology sections where a few isolated tangles in the amygdala may have easily been missed. Regardless of the exact ordering of events, both plausible directions of spread support a role for the amygdala as a vehicle of NFT spread within the MTL.

Establishment and further investigation of this amygdala-anterior hippocampal spread fosters several new research avenues, many of which use the same technologies that have begun to highlight the amygdala's role in Alzheimer's disease, as discussed earlier. For example, longitudinal tau-PET studies can be used to establish the association between tau-PET signal and accumulation in the different MTL regions, where a stronger link would be expected in tau-PET uptake and accumulation between the amygdala and anterior hippocampus than anterior hippocampus and anterolateral ERC. This could be complemented by ultra-high field imaging studies of the structural and functional connectivity patterns in these regions. Such a combinatorial approach would potentially allow for establishing the role of the amygdala in spreading of NFT pathology in the MTL, although it is inherently challenging to separate such small regions with the relatively low resolution of PET imaging. To establish the order of occurrence of pathology within these MTL regions, new statistical methods, such as EBM,[70] could be used in tau-PET datasets and ultimately also in growing post-mortem datasets with dense NFT staining in the MTL at different stages of the disease.[29,31]

A final research avenue is the investigation of whether the occurrence of such an additional pathway of NFT spreading is heterogeneous between patients. Four potential distinct trajectories of NFT deposition throughout the whole brain have been identified in a recent human *in vivo* study.[57] The question is whether such distinct trajectories for NFT spreading also exist within the MTL, with different patients typically exhibiting one of these distinct trajectories. The answer to this can potentially be addressed with longitudinal tau-PET studies. Furthermore, heterogeneity in the pathways of NFT spreading in the MTL could potentially explain clinical differences observed in the order in which symptoms appear in patients. For instance, more prominent NFT accumulation and spreading from the anterolateral ERC to the posterior hippocampus in the early stages would likely give rise to memory impairments as the first symptom,[71] as typically reported in Alzheimer's disease. In contrast, more prominent NFT accumulation in and spreading through the amygdala and anterior hippocampus might result in the earliest symptoms being neuropsychiatric in nature,[71] which has indeed been reported in a subset of Alzheimer's disease patients.[72] Hence, future areas of investigation rest not only in further solidifying the amygdala's role in the spread of NFT pathology throughout the MTL but also establishing the link of such a role for the amygdala to what we observe clinically in patients.

Implications of early amygdala involvement for Alzheimer's disease symptomatology

As the amygdala has been associated with different cognitive, emotional and behavioural processes,[73-76] early NFT accumulation in the amygdala may, at least partly, explain the occurrence of neuropsychiatric symptoms observed in Alzheimer's disease.[77,78] While NFT accumulation in the amygdala itself may play a role, NFT accumulation across the networks connected to the amygdala may also link to observed symptoms. This further underscores the important role an amygdala-anterior hippocampal circuit might play in Alzheimer's disease, as one example of an amygdala associated network. Indeed, as we speculated in the previous section, early NFT spread between the amygdala and anterior hippocampus may give rise to a 'neuropsychiatric-symptoms-first' subtype. In this section we will summarize different behavioural and emotional processes that the amygdala is implicated in, where we will focus on the amygdala nuclei and their functionality and discuss the functions of different amygdala networks (Benarroch,[79] Janak and Tye[80] and Kirstein *et al.*[81]). Subsequently, we will relate the reported functions of the amygdala to neuropsychiatric symptoms observed in early Alzheimer's disease and discuss future areas of research.

Functionality of amygdala nuclei and amygdala-associated networks

The amygdala consists of different nuclei that show striking morphological, connectional and developmental differences (Fig. 1B). Interestingly, there are some indications from animal and post-mortem studies supportive of a hypothesis of potential functional differentiation of the different amygdala nuclei (Fig. 1E). These hypotheses for functional differentiation are based on ablation studies in rodents and other animals, studies on receptor density of, for example, neurotransmitters in the different nuclei and studies on observed connectivity of the amygdala with other regions in animal studies. For example, the lateral, basal and central nuclei are implicated in fear and stress because of a high density of benzodiazepine receptors in the first two and of glucocorticoids receptors in the latter.[73-75] Regarding feeding behaviour, lesions in the central, medial and cortical nuclei result in a loss of appetite or thirst

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whereas lesions to the basolateral nucleus result in the opposite: excessive thirst or hunger. The basal, accessory basal and cortical nuclei have been implicated in motivational responses and reward behaviour because of their direct connections with the prefrontal cortex, including orbitofrontal and medial prefrontal cortices.[74] Moreover, behavioural studies in different mammals have suggested a role for the medial nucleus in aggressive, sexual and defensive behaviours.[74]

However, in order to understand the role of the amygdala, it is important to consider its role on a circuit or network level.[79,82,83] According to well established functional connectivity networks, the amygdala is part of the anterior MTL network,[71,82] which also includes the anterior hippocampus, the perirhinal cortex, temporopolar cortex and lateral orbitofrontal cortex. Components of the anterior MTL network including the anterior hippocampus have been implicated in assessing the significance of entities,[71,84] including functions such as emotional and reward processing, emotional memory and social cognition,[66,85-88] The amygdala is also part of a network consisting of inferior basal ganglia regions, the anterior cingulate cortex and the ventral tegmental area, which has been implicated in anhedonia and apathy.[89] A recent detailed study by Klein-Flügge and colleagues[82] characterized functional connectivity profiles of the whole amygdala, as well as its subregions, and investigated their relationship with four mental health dimensions—life satisfaction, negative emotions, sleep problems and anger. The results suggest a role for connectivity of the inferior-medial domain of the amygdala in anger and negative emotions, such as sadness. This association of the inferior-medial domain of the amygdala with fear and anger matches what is known from animal work and reports of receptor density.[73-75]

Based on this summary and given that NFT pathology has been mainly reported within the inferior-medial domain in the early stages of Alzheimer's disease, one could hypothesize that early neuropsychiatric symptoms in Alzheimer's disease, that are due to NFT accumulation in the amygdala and amygdala networks, could include changes in motivational (e.g. apathy), aggressive and sexual behaviour, changes in appetite, social cognition and in processing and memory of emotional stimuli as well as experiences of anger, anxiety, fear or depression.

Linking functionality of the amygdala's inferior-medial domain and networks to neuropsychiatric symptoms

In this section, we aim to link the functionality of the amygdala and associated networks to reported neuropsychiatric symptoms in the early stages of Alzheimer's disease. Neuropsychiatric symptoms are increasingly recognized as an important part of the clinical profile of Alzheimer's disease. Indeed, the first described Alzheimer's patient, Auguste Deter, was reported to have a range of prominent neuropsychiatric symptoms, including paranoia, anxiety, apathy and aggression.[90] Moreover, neuropsychiatric symptoms are now recognized to be early, and in some individuals, even among the earliest symptoms, according to the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework.[28]

Neuropsychiatric symptoms have also received renewed interest with the recently coined concept of mild behavioural impairment (MBI). MBI was introduced as a neurobehavioural analogue to MCI to capture the range of symptoms that occur in preclinical and early symptomatic Alzheimer's disease either alongside or sometimes in advance of cognitive complaints.[91,92] According to the provisional criteria, MBI is characterized by new onset and sustained neuropsychiatric symptoms that develop in advance of dementia. MBI symptoms have been reported in up to 10–15% of cognitively unimpaired older individuals and to be associated with greater cognitive decline.[92,93] MBI covers neuropsychiatric symptoms such as impaired drive and motivation (apathy), emotional dysregulation (mood and anxiety symptoms), impulse dyscontrol, agitation or abnormal reward salience (changes in response inhibition and self-regulation), social inappropriateness (impaired social cognition) and abnormal thoughts or perception (psychosis).[93] Some psychological symptoms (e.g. anxiety) might arise as reactive psychological symptoms to the early cognitive decline (i.e. coping and adjusting) and not always as sequelae of neurodegeneration.[94,95] However, these are not MBI; in this section, we consider primary neuropsychiatric symptoms, as described in the setting of MBI and their possible link to pathology and neurodegeneration in the amygdala and associated networks.

Based on the previous section ('Functionality of amygdala nuclei and amygdala-associated networks'), impaired drive and motivation, emotional dysregulation, social inappropriateness and perhaps agitation could be due, at least partly, to NFT accumulation in the amygdala and amygdala networks. Recent evidence showing an association of MBI with tau-PET signal in the MTL in cognitively unimpaired individuals is supportive of this notion and suggests that MBI can be an early manifestation of underlying neurodegenerative disease in advance of significant cognitive impairment.[77,92] Another recent study found a relationship between increased tau-PET signal in the MTL and depressive symptoms in cognitively normal older adults.[96] However, neither of these studies focused on tau-PET signal in the amygdala. To the best of our knowledge, only one study so far has looked at the association of neuropsychiatric symptoms and amygdala tau-PET uptake and did not find an association.[97] However, as this was an analysis in the Alzheimer's Disease NeuroImaging Initiative (ADNI) dataset, the results should be interpreted with caution as ADNI has restrictive inclusion criteria around mental health symptoms. Moreover, this study used the Neuropsychiatric Inventory, which is designed primarily to assess the spectrum of symptoms observed in dementia and not in earlier stages, such as the MBI checklist.[98] Hence, studies designed *a priori* to examine NFT pathology in the amygdala related to MBI are needed to definitely and robustly link these phenomena.

Overall, there is a growing literature on the occurrence of neuropsychiatric symptoms in early Alzheimer's disease that, strikingly, match the majority of the neuropsychiatric symptoms expected to follow from NFT accumulation in the amygdala. However, this observation is mostly circumstantial and requires direct linkage through neuroimaging studies of the amygdala, as discussed further in the next section.

Future directions for studying the role of the amygdala in neuropsychiatric symptoms of Alzheimer's disease

The aforementioned literature suggests a role for the amygdala and its associated networks in neuropsychiatric symptoms. However, much work is still needed to solidify and understand fully the association of NFT pathology in the amygdala and its associated networks and specific neuropsychiatric symptoms in Alzheimer's disease. In addition to supporting these findings with similar methods applied to additional cohorts, future research avenues include the analysis of tau-PET imaging in relation to different neuropsychiatric symptoms, the study of comorbid pathologies (co-pathologies) in the amygdala as alternative or complementary

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causes of neuropsychiatric symptoms, and the development of novel fMRI paradigms for analysing specific neuropsychiatric alterations against changes in specific nuclei of the amygdala or specific amygdala networks.

For instance, correlation of different symptoms with amygdala tau-PET signal could further solidify the specific link between neuropsychiatric symptoms and NFT accumulation in the amygdala and associated networks in Alzheimer's disease. Based on the above literature, one would expect changes in social cognition, apathy, anger, aggression, irritability, anxiety and depression, and sexual and eating behaviour to associate specifically with tau-PET signal in the amygdala (and associated networks) when occurring in the early stages of Alzheimer's disease.

Second, the amygdala has been cited not just as a hotspot for NFT pathology, but also of α-synuclein (the protein that accumulates in Lewy bodies and neurites) and transactive response DNA-protein (TDP) 43 pathology in Alzheimer's disease[99-101] (see Supplementary material, section 2 for a review of the literature on the distribution pattern of these co-pathologies in the amygdala). This thus indicates that the role other co-pathologies in the amygdala play in the development of neuropsychiatric symptoms should also be explored. For instance, α-synuclein pathology in the amygdala has been linked to visual hallucinations.[102-104] While these studies were not performed in cases with Alzheimer's disease, Lewy body pathology often co-occurs in Alzheimer's disease in the amygdala[99,105-108] and could potentially contribute to the occurrence of such symptoms. Interestingly, comorbid Lewy body pathology in the amygdala in Alzheimer's disease has also been linked to depressive symptoms.[109] While there are no PET measures for α-synuclein pathology yet, promising CSF measures are currently under development.[110,111] A future avenue of research would be to investigate if CSF measures of α-synuclein pathology, as a comorbid pathology, mediates a potential association between amygdala atrophy and depressive symptoms and hallucinations in the context of Alzheimer's disease. Relatedly, it would be of interest to gain a better understanding of the role of comorbid TDP-43 pathology in the amygdala in the context of Alzheimer's disease in the development of neuropsychiatric symptoms. Previous studies looking at the association of comorbid TDP-43 pathology with neuropsychiatric symptoms in patients with Alzheimer's disease neuropathologic changes showed inconsistent results.[112-114] Future studies are needed to investigate what role TDP-43 pathology in the amygdala plays in the symptom profile of Alzheimer's disease. Moreover, while not the focus of this review, the role of Aβ pathology, separate from NFT pathology, in the amygdala and associated networks in the development of neuropsychiatric symptoms should be further explored.

Finally, gaining a better understanding of the functional differentiation of the nuclei could lead to a better understanding of the symptomatology in Alzheimer's disease. However, research on the functional differentiation of amygdala subregions is still sparse and is usually not performed in living humans (but see Klein Flügge *et al.*[82]). In addition, amygdala nuclei are highly intertwined, which makes it inherently difficult to differentiate their functionality. Nevertheless, the pace of recent developments in ultra-high field imaging shows promise for elucidating the role of these different amygdala nuclei further.[81,115] In light of the evidence summarized here, these developments may thus foster, in parallel, intriguing new research avenues linking neuropsychiatric symptoms to amygdala shape changes in early Alzheimer's disease stages, which could be hypothesized to be localized to the inferior-medial domain of the amygdala, as reported in previous studies measuring shape change in the context of cognitive changes.[31,47] Another fascinating research avenue would focus on the development of new experimental fMRI paradigms that can probe neuropsychiatric alterations specific to amygdala changes in Alzheimer's disease. Indeed, studies have linked emotional memory changes, probed with experimental paradigms, to amygdala structure in the context of clinical (not biomarker confirmed) dementia of the Alzheimer's type.[116,117] These could be promising paradigms for studies with patients in early Alzheimer's disease stages, where the use of ultra-high field 7 T fMRI could potentially further allow us to spatially pinpoint the activation within the amygdala. Combining this with tau-PET imaging could provide even further insight into the role of Alzheimer's disease pathology in potential changes in emotional memory. Future studies should, however, go beyond emotional memory and develop fMRI paradigms for other neuropsychiatric alterations.

Conclusion

More than three decades after the paramount studies of Braak and Braak, Alzheimer's disease still harbours uncertainties with regard to its causes, mechanism and progression. As presented here, a body of evidence of early NFT pathology in the amygdala is emerging, echoing earlier post-mortem findings. Together with the amygdala's anatomical connectivity with areas of the ERC and anterior hippocampus and its association with neuropsychiatric symptoms observed in the clinical course of Alzheimer's disease, this evidence suggests the amygdala has a yet uncovered role in Alzheimer's disease and, therefore, should be a greater focus in Alzheimer's disease-related research. Indeed, the results from imaging studies point to the utility of amygdala imaging biomarkers for enrichment in clinical trials, for monitoring disease progression, or even for prognosis. The presented overview on amygdala connectivity, patterns of pathology accumulation, and functional architecture provide new insights into the mechanisms behind NFT pathology progression and symptom onset in Alzheimer's disease. It also generates new hypotheses of how to explain different symptom profiles in Alzheimer's disease, for example of the 'neuropsychiatric-symptoms-first' subtype, and to capture specific amygdala-focused vulnerabilities using functional imaging. Moreover, the amygdala as a potential second pathway of NFT spreading in the MTL provides future avenues of research by allowing for better modelling and understanding of NFT spread and the heterogeneity of NFT accumulation in the MTL, which will ultimately bring us one step further towards precision medicine in Alzheimer's disease.

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Competing interests

Under a license agreement between AnatomyWorks and the Johns Hopkins University, M.I.M. and the University are entitled to royalty distributions related to technology described in the study discussed in this. M.I.M. is a founder of and holds equity in AnatomyWorks. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. The remaining authors declare no conflicts of interest.

Supplementary material

Supplementary material is available at *Brain* online.

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