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2025

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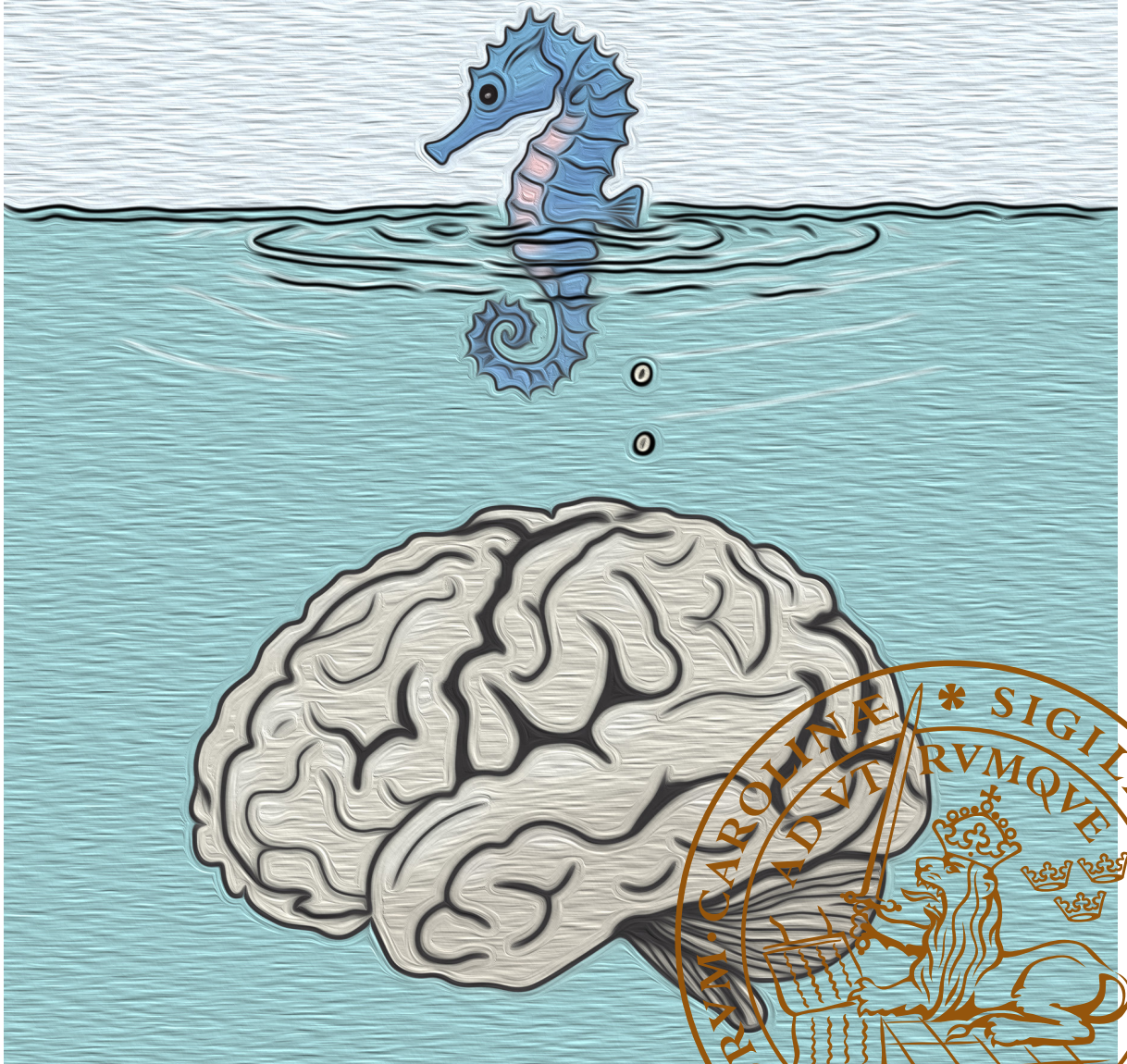
The medial temporal lobe in aging and Alzheimer's disease:
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Anika Lindblom-Wuestefeld

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Abstract: Alzheimer's disease, the most common form of dementia, is characterized by progressive cognitive decline and the accumulation of amyloid-beta (Aβ) and tau neurofibrillary tangle (NFT) pathology. The medial temporal lobe (MTL) is one of the earliest sites of NFT pathology, crucial for memory functioning, and is made up of cytoarchitectonic and functionally different subregions. These subregions are hypothesized to be differentially vulnerable to various neurodegenerative pathologies, such as NFTs. This thesis focuses on the MTL in aging and Alzheimer's disease. The two overarching objectives of this thesis were to (i) contribute to the methodological advancements of in vivo measures of MTL subregions and (ii) characterize MTL subregional atrophy and contributions to cognitive decline in aging and Alzheimer's disease.

In paper I, the variability in annotations of cortical MTL subregions on postmortem histology sections of different neuroanatomical laboratories were compared and characterized. The results increase our understanding of why differences in annotations arise, setting a crucial foundation for improved measurements and to study the MTL cortex with in vivo neuroimaging data. In paper II – part 1, a segmentation protocol for the whole amygdala on commonly used T1-weighted magnetic resonance images was developed. In paper III, Aβ-independent age-related tau pathology in normal aging was characterized. This study indicated that NFT pathology occurs in aging in MTL, frontal, and parietal regions, independent of Aβ, contributing to downstream effects of neurodegeneration and cognitive decline. In paper IV, specific structural measures were found to partially mediate the association between NFT pathology and cognitive subdomain associations, providing a nuanced understanding of region-specific macrostructural atrophy as one pathway of tau-induced cognitive changes. In paper II – part 2, MTL subregional atrophy patterns in amnestic early-onset versus late-onset Alzheimer's disease were investigated. The results showed that subtle MTL atrophy differences exist between these two groups. However, the patterns were not as distinct as previously reported, suggesting a largely shared pathophysiology for early- and late-onset Alzheimer's disease. In paper V, the relative contribution of NFT and TDP-43 pathology to MTL atrophy was reviewed. The findings were summarized to provide hypotheses on the interplay, synergism, and timing of the pathologies as well as future directions for research.

In summary, by developing and applying refined methodologies to characterize MTL subregions, this thesis contributes to a more detailed characterization of the complex factors driving MTL atrophy in aging and Alzheimer's disease. This will aid in the early detection and progression of Alzheimer's disease and allow fine-grained tracking of treatment outcomes in clinical trials.

Signature   Date 2025-05-06

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To David

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Original papers and manuscripts included in the thesis

I. **Wuestefeld A***, Baumeister H*, Adams JN, de Flores R, Hodgetts CJ, Mazloum-Farzaghi N, Olsen RK, Puliyadi V, Tran TT, Bakker A, Canada KL, Dalton MA, Daugherty AM, La Joie R, Wang L, Bedard ML, Buendia E, Chung E, Denning A, del Mar Arroyo-Jiménez M, Artacho-Pérula E, Irwin DJ, Ittyerah R, Lee EB, Lim S, del Pilar Marcos-Rabal M, Iñiguez de Onzoño Martin MM, Lopez MM, de la Rosa Prieto C, Schuck T, Trotman W, Vela A, Yushkevich P, Amunts K, Augustinack JC, Ding S-L, Insausti R, Kedo O, Berron D^, Wisse LEM^ (2024) Comparison of histological delineations of medial temporal lobe cortices by four independent neuroanatomy laboratories. *Hippocampus* 34:241–260. doi: 10.1002/hipo.23602

II. **Wuestefeld A**, Pichet Binette A, van Westen D, Strandberg O, Stomrud E, Mattsson-Carlgren N, Janelidze S, Smith R, Palmqvist S, Baumeister H, Berron D, Yushkevich PA, Hansson O, Spotorno N, Wisse LEM (2024) Medial temporal lobe atrophy patterns in early-versus late-onset amnestic Alzheimer's disease. *Alzheimer's Research & Therapy* 16:204. doi: 10.1186/s13195-024-01571-z

III. **Wuestefeld A**, Pichet Binette A, Berron D, Spotorno N, van Westen D, Stomrud E, Mattsson-Carlgren N, Strandberg O, Smith R, Palmqvist S, Glenn T, Moes S, Honer M, Arfanakis K, Barnes LL, Bennett DA, Schneider JA, Wisse LEM, Hansson O (2023) Age-related and amyloid-beta-independent tau deposition and its downstream effects. *Brain* awad135. doi: 10.1093/brain/awad135

IV. **Wuestefeld A**, Cui S, Xie L, McGrew E, Pichet-Binette A, Spotorno N, van Westen D, Mattsson-Carlgren N, Yushkevich PA, Das S, Wolk D, Wisse LEM, and for the Alzheimer's Disease Neuroimaging Initiative. Tau, atrophy, and domain-specific cognitive impairment in typical Alzheimer's disease. Manuscript under review at *Alzheimer's & Dementia*.

V. Wisse LEM, **Wuestefeld A**, Murray ME, Jagust W, La Joie R (2025) Role of tau versus TDP-43 pathology on medial temporal lobe atrophy in aging and Alzheimer's disease. *Alzheimer's & Dementia* 21:e14582. doi: 10.1002/alz.14582

Author's contributions to the papers

I.   Anika was part of the working group originally reviewing the different neuroanatomical annotations. She interpreted, together with Hannah Baumeister and supervisors, the results, created all figures, and drafted and revised the manuscript.

II.   Anika contributed to data preparation through quality assessment of the medial temporal lobe segmentations. She conducted all statistical analyses, interpreted the results together with co-authors, and drafted and revised the manuscript.

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IV.   Anika conducted all statistical analyses, interpreted the results together with co-authors, and drafted and revised the manuscript.

V.   Anika interpreted the results together with co-authors, created illustrations, and revised the manuscript.

Papers and manuscripts not included in the thesis

I. Baumeister H, Gellersen HM, Polk SE, Lattmann R, **Wuestefeld A**, Wisse LEM, Glenn T, Yakupov R, Stark M, Kleineidam L, Roeske S, Marcos Morgado B, Esselmann H, Brosseron F, Ramirez A, Luesebrink F, Synofzik M, Schott BH, Schmid MC, Hetzer S, Dechent P, Scheffler K, Ewers M, Hellmann-Regen J, Ersoezlue E, Spruth E, Gemenetzi M, Fliessbach K, Bartels C, Rostamzadeh A, Glanz W, Incesoy EI, Janowitz D, Rauchmann B-S, Kilimann I, Sodenkamp S, Coenjaerts M, Spottke A, Peters O, Priller J, Schneider A, Wiltfang J, Buerger K, Perneczky R, Teipel S, Laske C, Wagner M, Ziegler G, Jessen F, Duezel E, Berron D, for the DELCODE study group (2025) Disease stage-specific atrophy markers in Alzheimer's disease. medRxiv 2025.03.13.25323904. doi: 10.1101/2025.03.13.25323904

II. Baumeister H, Vogel JW, Insel PS, Kleineidam L, Wolfsgruber S, Stark M, Gellersen HM, Yakupov R, Schmid MC, Lüsebrink F, Brosseron F, Ziegler G, Freiesleben SD, Preis L, Schneider L-S, Spruth EJ, Altenstein S, Lohse A, Fliessbach K, Vogt IR, Bartels C, Schott BH, Rostamzadeh A, Glanz W, Incesoy EI, Butryn M, Janowitz D, Rauchmann B-S, Kilimann I, Goerss D, Munk MH, Hetzer S, Dechent P, Ewers M, Scheffler K, **Wuestefeld A**, Strandberg O, van Westen D, Mattsson-Carlgren N, Janelidze S, Stomrud E, Palmqvist S, Spottke A, Laske C, Teipel S, Perneczky R, Buerger K, Schneider A, Priller J, Peters O, Ramirez A, Wiltfang J, Heneka MT, Wagner M, Düzel E, Jessen F, Hansson O, Berron D (2024) A generalizable data-driven model of atrophy heterogeneity and progression in memory clinic settings. *Brain* 147:2400–2413. doi: 10.1093/brain/awae118

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V. Sadeghpour N, Lim SA, **Wuestefeld A**, Denning AE, Ittyerah R, Trotman W, Chung E, Sadaghiani S, Prabhakaran K, Bedard ML, Ohm DT, Artacho-Pérula E, Iñiguez de Onzoño Martin MM, Muñoz M, Molina Romero FJ, Delgado González JC, Jiménez M del MA, Rabal M del PM, Insausti Serrano AM,

González NV, Sánchez SC, de la Rosa Prieto C, Insausti R, McMillan C, Lee EB, Detre JA, Das SR, Xie L, Tisdall MD, Irwin DJ, Wolk DA, Yushkevich PA, Wisse LEM (2025) Developing an anatomically valid segmentation protocol for anterior regions of the medial temporal lobe for neurodegenerative diseases. *bioRxiv* 2025.02.11.637506. doi: 10.1101/2025.02.11.637506

Abstract

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Popular scientific summary

Aging is a normal biological process that affects all organs to some extent. The most complex organ of the human body is the brain, giving rise to our cognitive abilities and allowing us to function in everyday life. For some individuals, these cognitive changes are not "normal" and result in severe impairment of everyday functioning. This is called dementia. Dementia is a progressive disease linked to a gradual decline in cognitive abilities. Around 55 million individuals are affected by dementia worldwide, a number expected to rise in the coming years. Alzheimer's disease is the most common form of dementia where memory is primarily affected early in the disease before other cognitive impairments arise. This devastating condition is marked by the accumulation of harmful proteins, amyloid-beta (Aβ) and tau, in the brain.

The medial temporal lobe (MTL) is a small but very complex region in the brain responsible for a large portion of our memory functions. This region is affected early in the Alzheimer's disease process and specific subregions within the MTL are particularly vulnerable to tau accumulation or accumulation of other proteins, leading to the shrinking (atrophy) of these regions. This MTL atrophy has been shown to be associated with impaired memory functioning. Due to this, understanding the changes in the MTL is of high importance. This thesis delves into the intricacies of the MTL in both normal aging and Alzheimer's disease, aiming to refine our understanding of this brain region.

The overarching goal of this thesis was twofold: first, to improve the methods used to study the MTL using brain imaging, and second, to map the fine-grained changes in the MTL subregions and the relevance of these changes for cognitive decline in different aging populations.

Imagine trying to navigate a complex city with inaccurate maps, it would be quite difficult to find your way. This also applies when trying to investigate specific regions in the brain with inaccurate quantification measures. The first step was to study inconsistencies in how different neuroanatomists (scientists who study the brain structure) label and measure MTL subregions using brain tissue samples of deceased individuals. This study (paper I), compared these annotations, highlighting why discrepancies arise. This is crucial for establishing a reliable foundation for interpreting brain imaging data and ensuring everyone is using the same and

accurate "map". To advance methods further, we developed a method for measuring the amygdala, another MTL structure, using brain imaging (paper II – part 1).

In the next step, we focused on understanding how the MTL subregions are affected in aging and Alzheimer's disease. Understanding how tau accumulates in the brain can further allow us to comprehend the mechanisms underlying the disease and can thereby lead to better diagnosis and prognosis. The prevailing hypothesis is that tau pathology spreads across the brain in Alzheimer's disease only in the presence of Aβ, but this work (paper III) highlighted an independent accumulation of tau with a limited presence of Aβ. We demonstrated that tau can accumulate in the brain during normal aging, independent of Aβ, contributing to brain shrinkage (atrophy) and memory problems.

The accumulation of tau pathology has been associated with impaired cognitive function in previous studies. One hypothesis is that tau pathology leads to atrophy, which then affects cognitive abilities. However, it is unclear which brain regions are specifically involved. Building on this, paper IV investigated how brain atrophy in specific MTL regions is the pathway through which tau induces reduced functioning in different aspects of cognition. We found that certain structural changes in the brain partially explained the link between tau and specific cognitive decline, such as memory, revealing a more nuanced understanding of how tau disrupts cognition.

In paper II – part 2, the focus shifted to individuals that develop Alzheimer's disease at a much younger age (early-onset) and compared their patterns of MTL atrophy to individuals with the more common late-onset form of the disease. It has previously been reported that the MTL is not affected in these early-onset cases. However, there are different types of early-onset cases with different clinical presentations. We specifically focused on individuals that have memory deficits and compared these to late-onset cases that also show similar memory deficits. While subtle differences in MTL atrophy were found, the overall pattern of damage was remarkably similar, suggesting a shared underlying disease process between those two versions of memory-predominant Alzheimer's disease.

Finally, in paper V the intricate relationship between tau and another protein, TDP-43, in causing MTL atrophy was explored. This study reviewed knowledge and proposed new hypotheses about the interaction of these proteins. For example, both proteins could independently affect the MTL, interact together affecting the MTL, or one of the proteins may make the effects of the other more toxic, leading to faster decline. We suggest future research directions to understand which of the hypotheses is most likely in which cases.

By developing and applying refined methods to characterize the MTL, this research provides a more detailed picture of the factors driving brain damage, specifically in the MTL, in aging and Alzheimer's disease. This work will help to detect brain changes earlier and will allow us to track and potentially predict disease progression, making care more individualized.

Populärvetenskaplig sammanfattning

Att åldras är en normal biologisk process som påverkar alla kroppens organ i viss utsträckning. Det mest komplexa organet i människokroppen är hjärnan, som styr våra kognitiva förmågor och gör det möjligt för oss att klara av uppgifter i vardagen. När vi åldras försämras dessa förmågor, och för vissa individer är försämringen ''abnormalt'' stark, vilket kan medföra problem med till exempel minnet och att klara av vardagliga uppgifter. Detta kallas demens. Omkring 55 miljoner människor runt om i världen har i dagsläget drabbats av demens – en siffra som förväntas stiga under de kommande åren. Alzheimers sjukdom är den vanligaste typen av demens, där främst minnet påverkas tidigt i sjukdomsförloppet, följt av andra kognitiva nedsättningar. Alzheimers sjukdom kännetecknas av att två skadliga proteiner, amyloid-beta (Aβ) och tau, ansamlas i hjärnan.

Den mediala temporalloben (MTL) är en liten men mycket komplex region i hjärnan som är ansvarig för en stor del av våra minnesfunktioner. Denna region påverkas tidigt i Alzheimers sjukdom och dess mindre beståndsdelar (subregioner) är särskilt känsliga för ansamling av tau-proteinet, liksom för andra skadliga ämnen, vilket kan göra att subregionerna krymper och därmed leder till försämrad minnesfunktion. Eftersom MTL påverkas av Alzheimers sjukdom är det av stor vikt att förstå förändringarna som sker i regionen. Denna avhandling fokuserar på MTL i både normalt åldrande och Alzheimers sjukdom, med syftet att förbättra vår förståelse av denna del av hjärnan.

Målet för detta arbete har varit att bidra till vår förståelse för de förändringar som sker i MTL under normalt åldrande och Alzheimers sjukdom, vilka subregioner som påverkas och av vilka skadliga proteiner detta sker, och hur detta kan kopplas till kognitiva förändringar. För att nå detta mål, har även metoderna som används för att mäta MTL subregioner med hjälp av hjärnavbildning utvecklats.

Tänk dig att du försöker navigera med felaktiga kartor – sannolikheten för att du når din destination är då liten. Detta gäller även när man försöker undersöka regioner i hjärnan med felaktiga mått. Det första målet i avhandlingen var att undersöka olikheter i hur olika neuroanatomister (forskare som undersöker hjärnans struktur) skiljer på MTL-subregionerna på hjärnvävnadsprover från avlidna individer. Vi har därför jämfört deras annotationer och definitioner för att belysa varför avvikelser mellan neuroanatomister kan uppstå (artikel I). Att förstå dessa skillnader är avgörande för att kunna skapa en tillförlitlig grund och kunna tolka hjärnavbildningsdata, och därmed skapa en pålitlig ''karta'' för framtida forskning. För att ytterligare förbättra mätmetoderna som används på hjärnavbildningsdata, har vi även utvecklat en ny metod för att mäta MTL-strukturen amygdala (artikel II - del 1).

Utöver att bidra till metodutveckling, har vi fokuserat på att förstå förändringar i MTL-subregioner som sker under åldrande och Alzheimers sjukdom. Hur tau-

proteinet ansamlas kan vara viktigt för att bättre förstå sjukdomen, samt för att ge en korrekt diagnos och behandling. Den rådande hypotesen är att tau-proteinet sprider sig i hjärnan vid Alzheimers sjukdom endast när Aβ också ansamlas, men vårt arbete (artikel III) har belyst att tau-proteiner klumpar ihop sig även när det finns en begränsad närvaro av Aβ. Vi har visat att tau-proteinet kan ansamlas i hjärnan under normalt åldrande, oberoende av Aβ, och bidra till att hjärnan krymper (så kallad atrofi) och att minnesproblem uppstår.

Att tau-proteiner klumpar ihop sig är kopplat till försämringar av kognitiva funktioner. En hypotes är att detta sker eftersom tau leder till atrofi och att atrofin i sin tur leder till kognitiv svikt. Det är dock oklart vilka hjärnregioner som är inblandade. Med detta som utgångspunkt undersöktes i artikel IV om atrofi i specifika MTL-regioner bidrar till sambandet mellan tau-ansamling och försämring av olika kognitiva funktioner. Här har vi sett att vissa strukturella förändringar i hjärnan, speciellt i MTL-subregioner, delvis förklarat sambandet mellan tau och specifika kognitiva försämringar, till exempel minnet, vilket bidrar till en mer nyanserad förståelse för hur tau påverkar kognitiva funktioner negativt.

I artikel II - del 2 har fokus varit på individer som utvecklar Alzheimers sjukdom vid en yngre ålder än normalt. Det har tidigare rapporterats att MTL är mindre påverkad om man får sjukdomen i ung ålder. Hur atrofi i olika MTL-subregioner skiljer sig mellan unga och äldre individer som utvecklar Alzheimers sjukdom jämfördes. Eftersom det finns olika typer av tidiga debuter av Alzheimers sjukdom, har vi endast fokuserat på individer med minnesproblem. Vi har konstaterat att även om det fanns subtila skillnader mellan unga och äldre i hur MTL krympte, så var det övergripande mönstret av förändringar i MTL regionerna anmärkningsvärt likartade. Detta tyder på en gemensam underliggande sjukdomsprocess för dessa typer av Alzheimers sjukdom.

I artikel V undersöktes slutligen förhållandet mellan tau och ett annan protein, TDP-43, och hur dessa orsakar MTL atrofi. I denna studie har aktuell vetenskaplig litteratur granskats och från detta har hypoteser om hur dessa proteiner interagerar med varandra föreslagits. Till exempel kan båda proteinerna påverka MTL oberoende av varandra, de kan interagera, eller så kan ett av proteinerna intensifiera effekterna av det andra. Vi föreslår dessutom framtida forskningsinriktningar för att förstå vilken eller vilka av hypoteserna som är mest sannolik.

Sammanfattningsvis, genom att utveckla och tillämpa förfinade metoder för att karakterisera MTL subregioner ger denna avhandling en mer detaljerad bild av de faktorer som gör att speciellt MTL påverkas när vi åldras och i Alzheimers sjukdom. Denna avhandling bidrar till att utveckla metoder för att upptäcka förändringar i hjärnan tidigare, samt bidrar till forskningen som hjälper att spåra och potentiellt förutsäga förloppet av sjukdomen, vilket kan göra vården mer individanpassad.

Populärwissenschaftliche Zusammenfassung

Unser Gehirn ist für unsere kognitiven Fähigkeiten verantwortlich und ermöglicht uns somit das tägliche Leben zu bewältigen. Mit zunehmendem Alter treten einige kognitive Veränderungen auf. Bei manchen Menschen sind diese kognitiven Veränderungen nicht „normal" und führen deshalb zu einer schweren Beeinträchtigung der Alltagsfunktionen, was dann als Demenz bezeichnet wird. Demenz ist eine fortschreitende Krankheit. Weltweit sind ca. 55 Millionen Menschen von Demenz betroffen und es wird erwartet, dass diese Zahl in den kommenden Jahren drastisch steigen wird. Die Alzheimer Erkrankung ist dabei die häufigste Ursache für Demenz. Hier ist in erster Linie das Gedächtnis in einem frühen Stadium der Krankheit betroffen, bevor andere kognitive Beeinträchtigungen auftreten. Diese verheerende Krankheit ist vorwiegend durch die Ablagerung von schädlichen Eiweißen (Pathologien), insbesondere Amyloid-beta (Aβ) und Tau-Proteinen (Tau), im Gehirn gekennzeichnet.

Der mediale Temporallappen (MTL) ist eine kleine, jedoch anatomisch und funktionell sehr komplexe Region des Gehirns, die für einen großen Teil unserer Gedächtnisfunktionen verantwortlich ist. Der MTL ist im frühen Stadium der Alzheimer-Krankheit betroffen und Subregionen des MTL sind besonders anfällig für die Anhäufung von Tau und anderen Pathologien, welche zum Schrumpfen der Gehirnmasse (Atrophie) führen. Diese Atrophie wurde bereits durch frühere Forschung in Verbindung mit einer verschlechterten Gedächtnisfunktion gebracht. Daher ist das detaillierte Verständnis der Veränderungen innerhalb des MTL in der Alzheimer-Krankheit von großer Bedeutung.

Diese Doktorarbeit befasst sich mit den feinen Veränderungen des MTL, sowohl im Zuge des normalen Alterns als auch bei der Alzheimer-Krankheit. Zum einen war Fokus dieser Doktorarbeit die Verbesserung der Methoden zur Untersuchung des MTL mit Hilfe bildgebender Verfahren. Zum anderen bietet die vorliegende Arbeit anatomische Studie krankheits- und altersassoziierten Veränderungen der MTL-Subregionen und stellt deren Relevanz für den kognitiven Abbau in verschiedenen alternden Populationen dar.

Stellen Sie sich vor, Sie würden versuchen, sich in einer Stadt mit einer ungenauen Karte zurechtzufinden – an ein bestimmtes Ziel zu kommen wäre ziemlich schwierig. Dies lässt sich auch auf die Untersuchungen bestimmter Hirnregionen mit ungenauen Messmethoden übertragen. Der erste Schritt dieser Doktorarbeit bestand deshalb darin zu verstehen, wie verschiedene Neuroanatomen (Wissenschaftler, die die Struktur des Gehirns untersuchen) bestimmte MTL-Subregionen auf Hirngewebeproben von verstorbenen Personen definieren und die Subregionen voneinander unterscheiden. Im Rahmen dieser Studie (Artikel I) wurden diese Definitionen verglichen und die Gründe für entstandene Diskrepanzen identifiziert. Diese Untersuchung war erforderlich, um eine zuverlässige Grundlage

für die Interpretation von Bildgebungsdaten des Gehirns zu schaffen und sicherzustellen, dass alle Forschenden die gleiche und zuverlässige anatomische „Karte" verwenden. Zur weiteren Verbesserung der anatomischen Akkuratheit bildgebender Verfahren entwickelten wir eine neue Methode zur Messung einer bisher häufig unterfassten MTL-Region – der Amygdala (Artikel II – Teil 1).

Im nächsten Schritt dieser Doktorarbeit, fokussierten wir uns auf die Veränderungen der MTL-Subregionen während des Alterns und der Alzheimer-Erkrankung. Wie Tau-Pathologie sich im Gehirn ansammelt, kann uns wichtige Informationen über die Erkrankung geben, die zu einer korrekten Diagnose und Behandlung beitragen können. Die derzeit vorherrschende Hypothese ist, dass sich die Tau-Pathologie bei der Alzheimer-Krankheit nur in Anwesenheit von Aβ im Gehirn ausbreitet. Im Zuge dieser Doktorarbeit (Artikel III) wurde aber eine Anhäufung von Tau-Pathologie mit einer begrenzten Ausbreitung von Aβ gefunden. Wir konnten Hinweise dafür finden, dass sich Tau-Pathologie während des normalen Alterns unabhängig von Aβ im Gehirn ablagern kann. Diese Ablagerung kann wiederum zur Hirnatrophie und folglich zu Gedächtnisproblemen beitragen.

Die Ansammlung der Tau-Pathologie wurde in früheren Studien mit Beeinträchtigungen der kognitiven Funktionen in Verbindung gebracht. Eine Hypothese ist, dass Tau-Pathologie zu Atrophie führt, welche dann Einfluss auf die kognitiven Fähigkeiten hat. Es ist jedoch unklar, welche Gehirnregionen daran beteiligt sind. Darauf aufbauend wurde in Artikel IV untersucht, wie die Atrophie bestimmter MTL-Subregionen durch Tau zu einer verminderten Leistungsfähigkeit in verschiedenen kognitiven Bereichen führt. Basierend auf unseren Ergebnissen kommen wir zum Schluss, dass einzelne strukturelle Veränderungen im Gehirn den Zusammenhang zwischen Tau-Pathologie und spezifischen kognitiven Beeinträchtigungen, beispielsweise des Gedächtnisses, teilweise erklären. Diese Studie trägt somit zu einem differenzierteren Verständnis der komplexen Beziehungen von Tau-Pathologie und kognitiven Veränderungen bei.

In Artikel II – Teil 2 fokussierten wir uns auf Personen, die in einem relativ jungen Alter an Alzheimer erkrankten. In früheren Studien wurde berichtet, dass der MTL bei diesen früh auftretenden Fällen nicht betroffen ist. Wir konzentrierten uns hier speziell auf Personen, die im Rahmen der früh auftretenden Alzheimer-Erkrankung primär Gedächtnisdefizite aufzeigten, um diese mit Mustern der MTL-Atrophie der häufigeren, spät auftretenden Form der Alzheimer-Demenz zu vergleichen. Obwohl subtile Unterschiede in der MTL-Atrophie festgestellt wurden, war das Gesamtmuster der Atrophie bemerkenswert ähnlich. Dies deutet auf einen gemeinsamen zugrunde liegenden Krankheitsprozess der früh- und spät-auftretenden gedächtnisdominanten Alzheimer-Krankheit hin.

In Artikel V untersuchten wir schließlich die komplizierte Beziehung zwischen Tau-Pathologie und TDP-43 – einer weiteren Pathologie, die den MTL betreffen kann – bezüglich ihres Einflusses auf MTL-Atrophie. In diesem Artikel wurden die

derzeitigen Erkenntnisse hierzu zusammengefasst und neue Hypothesen über das Zusammenspiel beider Pathologien aufgestellt. Diese Hypothesen umfassen die unabhängige, gemeinsame und sich gegenseitig verstärkende Wirkung der Pathologien auf den MTL. Wir schlagen künftige Forschungsrichtungen und -vorhaben vor, um zu verstehen, welche der Hypothesen am wahrscheinlichsten ist.

Durch die Entwicklung und Anwendung verfeinerter Methoden zur Charakterisierung des MTL liefert diese Doktorarbeit ein detaillierteres Bild der Faktoren, die die Schädigung des Gehirns, insbesondere des MTL, während des Alterungsprozesses und der Alzheimer-Krankheit vorantreiben. Diese Arbeit bietet wichtigen wissenschaftlichen Fortschritt, der zu einer frühen Erkennung von abnormalen Hirnveränderungen beitragen kann. Darüber hinaus bietet sie wertvolle Erkenntnisse, die zur genaueren Überwachung und Prognose von Krankheitsverläufen genutzt werden können. Diese Fortschritte sind von enormer Bedeutung, um individualisierte Betreuungs- und Therapieansätze zu entwickeln.

List of abbreviations

Aβ	Amyloid-beta
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE	Apolipoprotein E
APOE-ε4	Apolipoprotein E ε4 allele
ASHS	Automated Segmentations of Hippocampal Subfields
CSF	Cerebrospinal fluid
DSM	Diagnostic and Statistical manual of Mental Disorders
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LATE-NC	Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
mPACC	Modified Preclinical Alzheimer Cognitive Composite
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NFTs	Neurofibrillary tangles
P-tau	Phosphorylated tau
PART	Primary Age-Related Tauopathy
PET	Positron-emission tomography
ROI	Region of interest
SDMT	Symbol Digit Modalities Test
SUVR	Standardized uptake value ratio

TDP-43   Transactive response DNA-binding protein 43 kDa

TMT   Trail-Making Test

WMH   White matter hyperintensities

Introduction

From normal aging to dementia

Aging is a natural process that occurs gradually over the course of the human lifespan as part of our biology [107]. This affects the physical function of all organs to some extent [107]. One of these affected organs is the brain, the most complex part of the human body [203, 276], which exhibits large inter-individual anatomical variability and varies in size. Atrophy, or the loss of brain cells and its connections, has been described in aging, albeit at a lower magnitude compared to neurodegenerative diseases, where widespread atrophy severely affects the brain and its functions [276]. This atrophy may also lead to loss or reduced efficiency of brain functions, such as cognition.

Cognition, defined as "the processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used" – Neisser [204], is a result of brain function [203]. Different domains of cognitive function exist and can be categorized [242]. For example in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [10] six domains are identified (i) perceptual-motor function, (ii) language, (iii) learning and memory, (iv) complex attention, (v) executive function, and (vi) social cognition [242]. Specific regions in the brain have been linked to different cognitive domains [229], for example the hippocampus is involved in memory function [83]. Cognition is not static and the aging process has been shown to affect cognitive domains at different ages [118, 276]. For example, age-related reductions in functions have been shown, such as episodic memory, executive functioning, and processing speed [63, 164, 244, 245, 271]. Yet, since age is the main risk factor of neurocognitive disorders, it is difficult to fully disentangle age-related cognitive changes from potential occurrences of pathologies in the brain at pre-symptomatic stages [41, 305].

A subgroup of aging individuals may experience a subjective change in cognitive functioning, while performing normally on standardized cognitive testing according to age- and education-specific norms [149]. This is called subjective cognitive decline (SCD, Fig. 1). Even though considered to function normally, some of these individuals have a higher risk to convert to mild cognitive impairment or dementia and more sensitive cognitive tests may be able to capture these subtle cognitive changes [176].
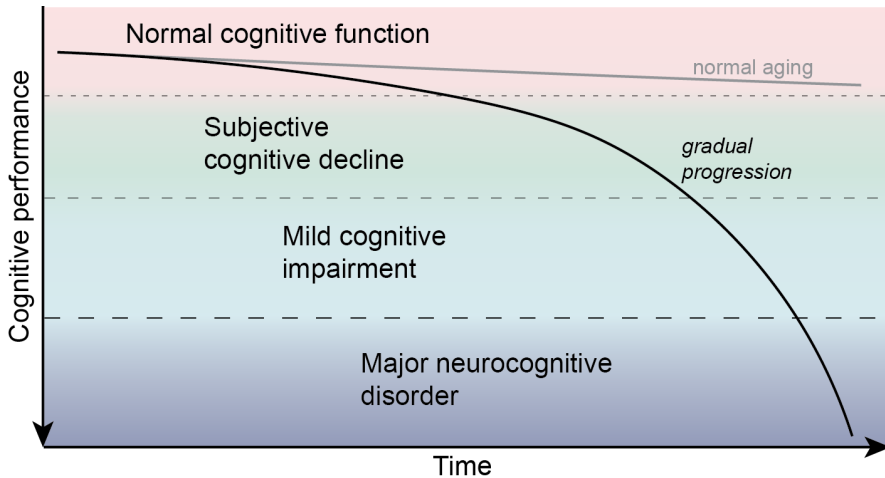
Fig. 1. From normal cognitive functioning to dementia.
A visualization of the progression from normal cognitive functioning to major cognitive disorder. Not all older individuals transition to having cognitive impairments, as indicated with a grey line indicating "normal" aging. The time to progress between the different stages differs among individuals.

Mild cognitive impairment (MCI), or mild neurocognitive disorder, describes the state between normal cognitive functioning and dementia [219] and has been reported to affect around 16% of individuals older than 70 years [41, 152]. Individuals with mild cognitive impairment exhibit cognitive symptoms that are not severe enough to classify as dementia disorder. Yet, they have objective cognitive impairment that exceeds the expected decline based on age and education level, without severely impacting activities of daily living (see Table 1 for the diagnostic criteria) [46, 96]. Between 16-65% of individuals with MCI develop dementia over the course of their lives. Especially, if amnestic symptoms are present, the risk to convert to Alzheimer's disease is increased [46, 96].

Finally, dementia, or, according to the DSM-5 [10], major neurocognitive disorder (see Table 1 for the diagnostic criteria), is a clinical syndrome causing cognitive deficits severe enough to interfere with activities of daily living [242]. Major neurocognitive disorder is an umbrella term of several different conditions and can be caused by many underlying diseases, such as Alzheimer's disease (characterized by amyloid plaques and tau pathology), frontotemporal dementia (characterized by tau pathology or Transactive response DNA binding protein 43 kDa), dementia with Lewy bodies (characterized by alpha-synuclein pathology) or vascular brain injury [242]. However, these underlying diseases are not mutually exclusive and can, thus, co-occur in a single individual [250]. The number of individuals living with dementia is expected to rise and is projected to amount to 139 million individuals worldwide in 2050 [8]. With a growing global elderly population, the study of

dementia and age-related changes in the brain has increasingly heightened societal significance [8, 9].

Table 1. Diagnostic criteria of mild and major neurocognitive disorders.
These definitions come from the DSM-5 [10] and are also reprinted here [242]. While criteria A and B differ from each other, criteria C and D apply to both disorders.

	Mild neurocognitive disorder	Major neurocognitive disorder
A	Evidence of a *modest* cognitive decline from a previous level of performance in one or more cognitive domain based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a *mild* decline in cognitive function, and 2. A *modest* impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence another quantified clinical assessment.	Evidence of *significant* cognitive decline from a previous level of performance in one or more cognitive domain based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a *significant* decline in cognitive function, and 2. A *substantial* impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence another quantified clinical assessment.
B	The cognitive deficits *do not* interfere with capacity for independence in everyday activities.	The cognitive deficits *interfere* with independence in everyday activities.
C	The cognitive deficits do not occur exclusively in the context of a delirium.	
D	The cognitive deficits are not better explained by another mental disorder.	

Alzheimer's disease

Alzheimer's disease is the most common form of dementia, accounting for up to 70% of dementia cases, according to the World Health Organization [307]. The disease was named after Alois Alzheimer, a German psychiatrist, who first described the pathological hallmarks of the disease; amyloid-beta (Aβ) plaques and tau neurofibrillary tangles (NFTs), which he first observed in his patient Auguste Deter in 1907 [7, 188].

Clinical symptoms

Alzheimer's disease is a clinic-pathological entity [134]. Clinically, Alzheimer's disease is characterized by progressive cognitive decline that occurs over many years and has an insidious onset [163]. The cognitive domain affected most often and earliest is memory, and deficits in other functions – such as language, executive function, and visuospatial abilities – develop during the course of the disease [163].

In order to assess cognitive symptoms, neuropsychological testing is commonly used. Paper-pencil tests constitute the most widely used form of cognitive assessment [44, 183]. For each of the cognitive domain listed in the previous section, different subdomains exist for which specific cognitive tests are available [270].

Neuropsychologists commonly look at a collection of different tests to measure specific cognitive functions [72]. Central to this thesis is episodic memory, which is defined as recollections of lived experiences [39]. This is commonly assessed using lists of words that are read or shown to a patient, and they are asked to memorize and repeat back those words immediately over several trials and after a time delay (delayed recall) [39, 175]. Alternatively, stories are read to a patient, which they are asked to re-tell immediately or after a time delay [39, 175]. Given the complexity of human cognition, a wide variety of tests exist that cover all the six cognitive domains [175, 270]. Of importance, cognitive tests commonly assess more than one cognitive function [175, 270]. For example, the described word list learning task does not only measure episodic memory functioning but also requires language and attention. In order to disentangle which cognitive function is affected, a comprehensive test battery is needed [175]. In research it is also common practice to define global cognition by combining scores of different cognitive tests into one score, as has been done for the assessment of preclinical Alzheimer's disease [72]. Note, that the ecological validity of traditional cognitive tests has been questioned, as the tests not necessarily directly reflect everyday tasks [175].

Hallmarks of Alzheimer's disease

Alzheimer's disease is characterized by two hallmark pathologies: extracellular Aβ plaques and intracellular neurofibrillary tangles (NFTs, Fig. 2).
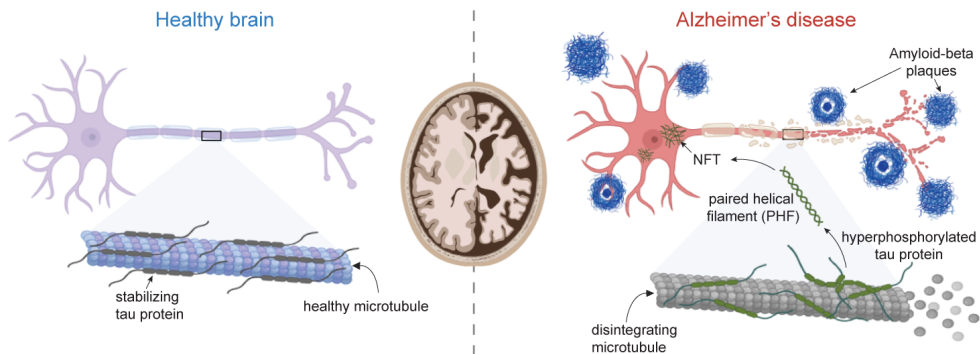
Fig. 2. Overview of Alzheimer's disease pathology.
Overview of a healthy brain (left panel) compared to Alzheimer's disease pathological processes in the brain (right panel) showing extracellular Aβ plaques and intracellular neurofibrillary tangles. Abbreviations: NFT=neurofibrillary tangle. Figure created with Biorender.

Amyloid-beta plaques

Aβ deposits of different types have been found of which dense-core and diffuse plaques are the most common types in Alzheimer's disease [196, 250]. The Aβ proteins are formed by the cleavage of the amyloid precursor protein (APP), which

is processed in two different pathways [48]. One of these pathways (= the amyloidogenic pathway), results in the production of different lengths of monomeric Aβ peptides [48]. Even if the function of Aβ in its monomeric form is unclear, these soluble monomeric Aβ peptides are generated in healthy brains [109] where the most abundant fragments are the 40-amino acid and 42-amino acid Aβ isoforms (Aβ40 and Aβ42, respectively) [48].

Likely due to an imbalance between production and clearance of Aβ peptides in Alzheimer's disease, these monomeric peptides are aggregating into oligomers, protofibrils and then finally insoluble fibrils, which are the major components of Aβ plaques (Fig. 2) [48]. These plaques can be found widespread across the brain. A staging system of the initial occurrence in the neocortex and subsequent spread of Aβ across the brain has been proposed and is widely accepted, called Thal stages (Fig. 3) [279]. With increasing disease stages (disease progression), Aβ plaques continuously impact and reduce neuronal integrity [35, 132].

Aβ has been shown to accumulate into plaques 10-30 years prior to onset of Alzheimer's disease dementia [111]. Aβ pathology is present in around 30% of individuals older than 70 years and without apparent cognitive decline [143]. Individuals that are Aβ-positive (i.e., have sufficient Aβ pathology to pass a set threshold of positivity) but have intact cognition, are at greater risk of subsequent cognitive decline [143]. Due to this observation, some experts consider these individuals to be in an asymptomatic or preclinical phase of Alzheimer's disease [71, 163], although others argue that Aβ pathology alone, without cognitive impairment is not sufficient to give such a label [76].

Aβ plaques can be evaluated postmortem in brain sections of deceased individuals, by the use of certain dyes that stain Aβ plaques [125]. Additionally, Aβ pathology can be assessed in vivo by analyzing proteins in cerebrospinal fluid (CSF), the liquid filling the ventricles and cerebral and spinal subarachnoid spaces of the central nervous system [294]. CSF Aβ was the first available biomarker of Alzheimer's disease [187]. It has been shown that levels of Aβ pathology can be reliably measured [111] and reduced CSF Aβ levels are believed to reflect higher levels of Aβ plaques in the brain [87]. CSF Aβ42, preferably used as a ratio with Aβ40 to normalize for inter-individuals CSF variability, has been shown to be able to indicate early pathological changes [111]. Recently, also blood-based biomarkers of Alzheimer's disease pathologies have become available [113]. While this advancement is worth mentioning and an important step for Alzheimer's disease research and clinical practice [113], a detailed discussion is beyond the scope of this thesis. Yet, also other methods of assessing Aβ pathology in vivo using positron emission tomography are available and will be discussed below.
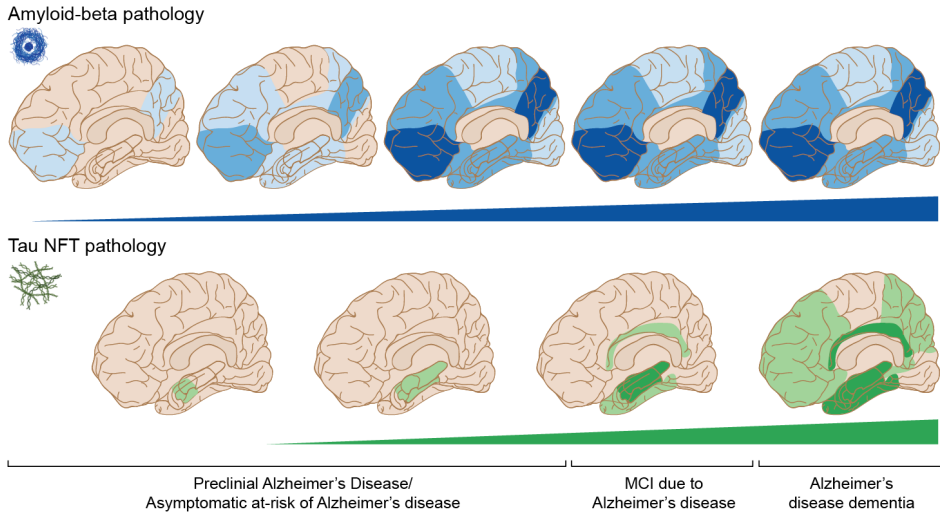
Fig. 3. Overview of assumed spreading of Alzheimer's disease pathologies.
Overview of spatiotemporal spreading stages of extracellular Aβ plaques (top) and intracellular NFTs (bottom). Based on [35, 156, 279]. Abbreviations: MCI=mild cognitive impairment; NFT=neurofibrillary tangle.

Tau neurofibrillary tangles

Tau is a protein that is normally phosphorylated which allows its involvement in microtubule stabilization and assembly along the neuronal axons [293] and is encoded by the MAPT gene [290].

In Alzheimer's disease, and other neurodegenerative diseases, tau proteins can become abnormally hyperphosphorylated which leads to detachment from the microtubule (Fig. 2) [90, 106]. This process can occur at different phosphorylation sites and leads to aggregation of misfolded tau [65, 105, 163] into paired helical filaments (PHFs), which in later stages form NFTs [90, 106] and neuropil threads [35, 132]. As mentioned above, this tau pathology accumulates intracellularly [163]. The occurrence of PHFs, NFTs, and neuropil threads lead to a disruption of the axons and to degeneration of neurons [98]. NFTs are initially appearing as pre-tangles, then developing into mature tangles, which affect the nucleus of the neuron, and eventually leading to the death of the neuron, leaving behind an extracellular ghost tangle [199]. This occurrence of NFTs is the second hallmark of Alzheimer's disease pathology but they also occur in other tauopathies (neurodegenerative diseases characterized by misfolded tau protein aggregation) [59]. Different tau isoforms exist, which can be categorized into 3R and 4R tau, since they contain either three or four microtubule binding repeats [163, 290]. 3R and 4R tau isoforms are differently predominant in different tauopathies [163, 290]. In Alzheimer's disease, a mix of both 3R and 4R tau is present [90, 163]. In this thesis, NFTs and

neuropil threads will be referred to as NFTs for the sake of clarity and to enhance readability of the text.

NFTs are also thought to occur in a typical spatiotemporal pattern (Fig. 3). The first cortical deposition of NFTs is in the transentorhinal cortex of the medial temporal lobe, prior to spreading to other regions within the medial temporal lobe, such as the entorhinal cortex and Cornu Ammonis 1, and subsequently spreading along the parietal and frontal cortices [35, 36]. Due to this first occurrence of NFTs in the medial temporal lobe, this region is of high importance to understand the pathophysiology of Alzheimer's disease. A detailed description of the medial temporal lobe will be given below. Six stages of NFT spread are widely accepted, also called Braak stages [35, 36]. The presence of NFTs may occur in the (trans-)entorhinal cortex in "normal" aging [38] but is thought to spread from the medial temporal lobe to other cortical regions in the presence of Aβ pathology, which is called the "amyloid cascade hypothesis" [115]. This means that Aβ pathology is hypothesized to be required for NFTs to start to spread outside the MTL across the brain, although exact mechanisms remain elusive [62, 119, 150, 226]. One current hypothesis is that this spread of NFT occurs prion-like, by spreading through connected neurons [37, 51, 137, 174].

Of importance is also that the NFT accumulation in Alzheimer's disease is more closely linked to atrophy of the brain's neuronal cell bodies and dendrites and subsequent cognitive decline than Aβ pathology [21, 28, 167, 205, 312]. This atrophy usually occurs first in the medial temporal lobe and then extends to parietal and frontal regions [223].

As for Aβ pathology, postmortem staining of NFTs enables the investigation of tau pathology in the brain [199]. In CSF, both total tau and phosphorylated tau (p-tau) can be measured [111]. While total tau is thought to represent global neurodegeneration, p-tau is more Alzheimer's disease-specific [111, 286]. Tau species that are most studied in CSF are p-tau181 and p-tau217, which have been shown to reflect both Aβ and tau pathology. P-tau217 is the more promising marker for later disease stages and thereby more related to tau pathology [111]. Additionally, several head-to-head studies showed the utility of p-tau217 as a biomarker, leading to a rapid translation into clinical practice [111, 142]. Measures more closely related to tau are in development and are being further evaluated [124]. In vivo positron emission tomography evaluation of NFT pathology will be discussed in the next sections.

The progression of Alzheimer's disease

Reflecting its progressive nature, Alzheimer's disease is best understood as a continuum, similar to that depicted in Fig. 1. Alzheimer's disease usually begins with a preclinical stage where individuals show pathological changes typical for

Alzheimer's disease but their cognitive function remains unaffected [163, 262]. This can be followed by, the above mentioned, MCI where cognitive changes occur and finally results in dementia, with severe impairments in cognitive functioning and activities of daily living [163]. There are ongoing debates on the exact naming of these stages (for example, preclinical Alzheimer's disease versus asymptomatic at-risk) and if the presence of underlying pathology without cognitive symptoms is sufficient to diagnose someone with Alzheimer's disease [75, 136, 221]. Individuals that are suspected to have underlying Alzheimer's disease pathology and exhibit cognitive symptoms can be diagnosed with Alzheimer's disease dementia during life. However, a definite Alzheimer's disease diagnosis can only be fully confirmed after death upon neuropathological investigation of the brain [220]. Yet, technological advancements make it possible to investigate the presence of the Alzheimer's disease hallmarks in vivo and this has since been incorporated in the diagnostic criteria [75, 136].

Types of Alzheimer's disease

The majority of Alzheimer's disease cases are sporadic, meaning they are not autosomal dominantly inherited, though genetic susceptibility remains a risk factor. Sporadic Alzheimer's disease has two subtypes: (i) late-onset and (ii) early-onset [139] but their exact cause is unknown [139]. The later in life occurring type, late-onset sporadic Alzheimer's disease is more common and usually defined by an onset of symptoms above 65 years of age [139]. On the other hand, the less frequent early-onset sporadic Alzheimer's disease constitutes about 5-10% of the cases and is defined by the onset of symptoms prior to 65 years of age. These individuals are less likely to carry the mutation of the risk gene Apolipoprotein E (*APOE*, allele ε4) and have been shown to present with non-amnestic symptoms more often [193]. Yet, different phenotypes of early-onset sporadic Alzheimer's disease exist [193], which have commonly been grouped together in research focusing on early-onset sporadic Alzheimer's disease. Worth mentioning even though not the focus of this thesis, autosomal dominant AD, constituting around 1% of all Alzheimer's disease cases and is caused by a genetic mutation of three different genes that increase the production of Aβ (i.e., presenilin 1 or 2, and amyloid precursor protein) [16].

Co-pathologies in Alzheimer's disease

Even though Aβ plaques and tau NFTs are the primary hallmarks of Alzheimer's disease, it has been shown that co-pathologies (i.e., co-occurring pathologies) are common in individuals with Alzheimer's disease [157, 165]. These co-pathologies are usually cerebrovascular disease pathologies, such as infarcts, small vessel disease, atherosclerosis, or cerebral amyloid angiopathy, or other neurodegenerative pathologies, such as Transactive response DNA-binding protein 43 kDa (TDP-43),

and alpha-synuclein (α-synuclein) pathology, which appear to increase with increasing age [139, 157, 158]. Two of these pathologies are investigated in this thesis: small vessel disease and TDP-43.

Small vessel disease associated cerebral white matter lesions can be seen on structural MRI as hyperintense signal on Fluid attenuated inversion recovery T2-weighted sequences (T2w FLAIR) and can be quantified, for example in total white matter hyperintensity volumes [228]. Their etiology is not fully understood but one hypothesis is that they are due to ischemia causing axonal loss and demyelination [189, 228].

Abnormally phosphorylated TDP-43 leads to neuronal TDP-43 inclusions [190]. TDP-43 is the protein that is the primary pathology in part of the cases with fronto-temporal lobar degeneration (FTLD) [103, 209] and in Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) [207]. LATE is characterized by an amnestic profile, advanced age, TDP-43 accumulation in the medial temporal lobe, and is linked to hippocampal sclerosis [207]. This proteinopathy has been shown to co-occur in Alzheimer's disease in 13-78% of the cases [280, 295], which is associated with steeper atrophy and cognitive decline rate [159], and a potential link between NFTs and TDP-43 type-β has been proposed [190]. Yet, due to the lack of reliable in vivo biomarkers of TDP-43, the investigation of concomitant TDP-43 pathology in Alzheimer's disease has been challenging [306]. While the investigation of in vivo biomarkers is ongoing, several structural MRI biomarkers have been proposed, such as the ratio of regions typically affected and unaffected by TDP-43 pathology [306]. One of these was utilized in this thesis [93].

Primary age-related tauopathy

The above explained spatiotemporal spreading pattern of NFTs pathology starting in certain medial temporal lobe subregions prior to spreading across the neocortex has been widely accepted. However, the occurrence of NFTs in the aging brain has been shown with minimal presence of Aβ pathology [38, 133, 147, 317]. Since some of these individuals with NFTs in the absence of Aβ pathology exhibit cognitive impairment, the concept primary age-related tauopathy (PART) was established [58].

PART is defined as pathological accumulation of NFTs in Braak stages I to IV, in the absence or with limited presence of Aβ pathology, associated with memory decline [58]. Even though NFTs can occur up to Braak stage IV (medial temporal lobe, as well as fusiform, lingual, and middle temporal gyri [33]), it is hypothesized that NFT pathology in PART is typically limited to the medial temporal lobe [58]. Differences in cognitive impairment compared to Alzheimer's disease has been described in PART with a slower and milder progression [22, 29, 146, 154, 277]. In

these cases, less *APOE* ε4 and more ε2 carriership, and lower levels of TDP-43, α-synuclein, and Lewy body pathologies have been observed [22, 122]. However, similarly to Alzheimer's disease, TDP-43 pathology has been found to be present in around 30% of PART cases [154]. Moreover, a structure-based classification of tauopathies indicates the same structure of tau for both Alzheimer's disease and PART [247, 256] and similar transcriptional changes [266]. Thus, debates are ongoing on whether PART is its own entity or whether it should be considered a form of Alzheimer's disease [80, 122]. More research is required to understand if these syndromes are distinct entities, and the second-generation tau-PET tracers are one way to advance this investigation in vivo.

The medial temporal lobe

The medial temporal lobe (MTL), most well-known for its role in memory function [83, 239, 265], is a complex structure made up of cytoarchitectonic and functionally different subregions [36, 42, 69, 130, 131, 283]. The MTL has been scrutinized in various fields, such as cognitive neuroscience to understand how the memory system works [84, 265]. Additionally, the MTL is of importance in different populations, such as aging [74, 91, 210, 234], epilepsy [26, 73, 77], posttraumatic stress disorder [25, 121], and dementia [3, 92, 301, 320]. Amnestic symptoms are hallmark symptoms of Alzheimer's disease and other dementias [86, 163], underscoring the need to characterize structural MTL and molecular changes to better understand the pathophysiology and progression of the diseases. This section presents an overview of the anatomical characteristics of the MTL, discusses the functions of subregions, as well as its vulnerability to pathologies in aging and dementia.

Anatomy

As the name indicates, the MTL is located in the medial part of the temporal lobe (Fig. 4). The MTL comprises the hippocampal formation, the amygdala, and surrounding cortical regions on the ambient and parahippocampal, and in some definitions, fusiform gyri [69] (Fig. 4B). These regions are variable in their composition, ranging from 3-layered allocortex anteromedially to 6-layered isocortex laterally [88, 131, 283, 284] (Fig. 4C).

A Anatomical terms of location

coronal plane
sagittal plane
axial plane

superior/dorsal
posterior/caudal
lateral
medial
anterior/rostral
inferior/ventral

B Medial temporal lobe anatomy

i

ii

Cornu Ammonis 3
Cornu Ammonis 2
Cornu Ammonis 1
Dentate gyrus
Subiculum

anterior
posterior

lateral ◄──► medial

Amygdala | Hippocampal formation | Entorhinal cortex | Brodmann area 35 | Brodmann area 36 | Parahippocampal cortex

C Cortex types in the medial temoral lobe

sulcus semiannularis

Amygdala

Hippocampal formation

Parahippocampal gyrus

Sulcal fundus

collateral sulcus
Crown of fusiform gyrus
occipitotemporal sulcus

lateral ◄──► medial

external layers
I II III IV V VI
internal layers

Granularity

Agranular
Lacks granule cell bodies
Dysgranular
Exhibits few loosely packed granule cells
Granular
Prominent and densly packed granule cell layer

Cortex type

Allocortex
Three-layered cortex
Periallocortex
Six-layered agranular cortex
Proisocortex
Six-layered dysgranular cortex in which not all isocortical features are clearly expressed
Isocortex
Six-layered granular cortex showing organized interal and external granule cell layers

D Connectivity

Amygdala

Entorhinal cortex
Layer II
Layer III

Hippocampal formation
Dentate gyrus
Cornu Ammonis 3
Cornu Ammonis 1
Subiculum

Input from cortical regions
Input from subcortical regions
Output to subcortical regions
Output to cortical regions

Brodmann area 35
Brodmann area 36
Parahippocampal cortex

Fig. 4. Overview of relevant anatomical terminology and MTL anatomy.
A: Overview of relevant anatomical terms of location within the human brain. **B**: Overview of location of MTL subfields in the brain and their location to each other (**Bi)** as well as a coronal section of the MTL subfields (**Bii**). **Bii** shows a coronal cross-section of the MTL subregions. **C**: Overview of additional terminology, such as cortex type on a coronal cross-section of the MTL, more anterior to the cross-section of Bii. Note that borders may vary between subjects. **D**: Overview of connectivity between regions (for more detail see [4, 30, 127, 130, 170, 273]).

35

The hippocampal formation

The hippocampal formation is 4 to 5 cm long and was named after the marine animal 'seahorse' [78, 127]. It extends along the longitudinal axis of the brain (anterior to posterior) and has an elongated u-shape from the sagittal view (Fig. 4B), giving rise to its name [78]. Along the longitudinal axis, the hippocampal formation can be divided into three neuroanatomic parts: (i) the hippocampal head, (ii), the hippocampal body, and (iii) the hippocampal tail [79]. The hippocampal formation is classified as allocortex (i.e., 3-layered cortex) and is made up of distinct cytoarchitectonic and interconnected substructures or subregions, that are interconnected, making up a functional unit: the Cornu Ammonis, dentate gyrus, and subiculum [64, 79, 127].

The Cornu Ammonis and dentate gyrus are the two parts of the hippocampal formation creating its characteristic shape in coronal view, as they are formed as two interlocking Cs [127]. The Cornu Ammonis can be divided into three distinct cytoarchitectonic regions (Cornu Ammonis 1-3) [127]. The Cornu Ammonis 1, the biggest and most complex subregion, has a characteristic thick pyramidal cell layer. The Cornu Ammonis 1 borders the Cornu Ammonis 2 inferiorly and the subiculum laterally in a stereotypical hippocampal body slice. Cornu Ammonis 2, located between Cornu Ammonis 1 and 3, is characterized by a compact, narrow pyramidal layer [127]. Cornu Ammonis 3, located between Cornu Ammonis 2 and the dentate gyrus, is characterized by the largest pyramidal cells compared to the other subregions [127].

The dentate gyrus, instead, is characterized by a granule cell layer [127]. Note that there has been some controversy around the third layer of the dentate gyrus and whether this should be called Cornu Ammonis 4 instead [79, 127]. The dentate gyrus is also one of the regions in the brain where neurogenesis, the production of new neurons, occurs, but the entire hippocampal formation has been shown to have high plasticity [261, 274].

Finally, the subiculum is the transitional region between the hippocampal formation (3-layered allocortex) and the 6-layered cortex [127]. The subiculum consists of a characteristic pyramidal cell layer [127] and can be divided into the following subdivisions: the subiculum proper (3-layered allocortex), presubiculum and parasubiculum (both 6-layered periallocortex) [67].

The amygdala

The amygdala is shaped like an almond and located in the temporal lobe, anterosuperior to the hippocampus (Fig. 4) [231, 269]. The amygdala consists of several subnuclei with a similar complexity as hippocampal subfields [170], which goes beyond this thesis. Albeit the amygdala is showing tau pathology in early stages of Braak's staging system, it has been studied less in Alzheimer's disease, but has received more attention in recent years [269].

Extra-hippocampal MTL cortex

The extra-hippocampal MTL cortex consists of the entorhinal cortex, the perirhinal cortex (Brodmann areas 35 and 36) as well as the parahippocampal cortex (a cytoarchitectonic distinct cortical region, not to be confused with the parahippocampal gyrus, which is the gross anatomical term for the gyrus adjacent to the hippocampus encompassing all these structures; Fig. 4). As mentioned above, these subregions are located on the ambient, and parahippocampal, and in some definitions, fusiform gyri [69, 128]. Important landmarks include the collateral and occipitotemporal sulci (Fig. 4C). The collateral sulcus is located between the parahippocampal and fusiform gyrus [233, 267]. The occipitotemporal sulcus is located between the fusiform gyrus and the inferior temporal gyrus (also called occipitotemporal gyrus) [216].

The entorhinal cortex corresponds to Brodmann areas 28 (on parahippocampal gyrus) and 34 (on ambiens gyrus) [42]. The entorhinal cortex is located on the anterior part of the parahippocampal and ambiens gyri and borders the subiculum at the height of the hippocampal formation (Fig. 4) [79, 127]. It is surrounded by Brodmann area 35 ($\approx$ transentorhinal cortex) anteriorly, posteriorly, and laterally, and is often located on the medial bank of the collateral sulcus. Anterior to the hippocampus, the entorhinal cortex is adjacent to the periamygdaloid cortex [127]. The entorhinal cortex is 6-layered periallocortex (i.e., lacking granule cell bodies) and is characterized by layer II cell islands as well as a *lamina dissecans*, an agranular cell layer [127, 130, 131, 268].

Brodmann area 35 is also called perirhinal cortex, but has in some definitions been described as being part of the perirhinal sulcus, grouped together with Brodmann area 36 [14, 273]. It is bordering the entorhinal cortex anteriorly, laterally, and posteriorly (Fig. 4) [14, 42, 273]. Brodmann area 35 is located adjacent to the entorhinal cortex [14] and is located on the medial and/or lateral banks of the collateral sulcus, depending on the depth of that sulcus and can, thus, end laterally on the bank of the occipitotemporal sulcus [14, 69]. Brodmann area 35 has been described as periallo- and proisocortex (i.e., 6-layered cortex with agranular or dysgranular cortex) [14, 34, 69] and maps closely to the transentorhinal cortex as described by Braak and Braak [36].

Brodmann area 36, also entitled ectorhinal cortex, borders Brodmann area 35 laterally as well as anteriorly and posteriorly [14, 69, 284] and has been described as proisocortex and isocortex (6-layered dysgranular and granular cortex) [69, 70]. In this thesis, Brodmann areas 35 and 36 are considered separate regions.

Lastly, the parahippocampal cortex borders the perirhinal and entorhinal cortex posteriorly (Fig. 4). It is located posterior to the entorhinal cortex and Brodmann areas 35 and 36 on the parahippocampal gyrus, occupying the medial bank of the collateral sulcus. This region has been historically less studied compared to the other cortical MTL subregions [267] and comprises periallo- and proisocortex [69, 267].

In some work parahippocampal cortex also includes isocortex laterally, extending beyond the medial bank of the collateral sulcus [267]. The parahippocampal cortex includes subregions TH (medial) and TF (lateral) [69], but other names are used as well [308].

Two important aspects need to be considered. First, even though descriptions and demarcations of these regions are possible, there is variability between neuroanatomical schools as becomes clear by reading the literature [e.g., 14, 67, 127, 273]. Second, it is important to be aware that there is substantial heterogeneity in the presentation of these structures [69, 129, 192, 213]. This heterogeneity is partly due to the variability in depth and ramification of the collateral sulcus, influencing the precise locations of the cortical MTL subfields and, additionally, large heterogeneity also exists for the hippocampal formation and the amygdala [69, 129, 275]. These aspects make the demarcation challenging. Based on these anatomical distinctions, segmentation tools have been developed but continuous improvement of these methods, translating neuroanatomical knowledge to neuroimaging, is ongoing, e.g., the Hippocampal Subfields Group (https://hippocampalsubfields.com/).

Connectivity

In order to understand how the above-described MTL subregions work together, the connectivity between the regions needs to be considered. The MTL subregions have internal connections with each other [4, 127, 130]. For example, the regions within the hippocampal formation are interconnected and receive input from the extra-hippocampal MTL regions [4, 127, 130]. Additionally, the MTL subfields both receive input and relay output to several subcortical and cortical regions [30, 170, 269, 273]. A detailed description is beyond the scope of this thesis; however, a schematic summary of some connections is given in Fig. 4D. Since the MTL is connected to other brain regions, it indicates that the MTL does not function independently from the rest of the brain. Instead, the brain, including the MTL, functions in networks [255]. One of the most widely used models including the MTL is the anterior-temporal versus posterior-medial network organization, connecting the MTL and its functions to the rest of the brain [232, 239]. Connectivity was not directly investigated in this thesis but is important to mention, as it may have implications for the hypothesized prion-like spread of NFTs [51, 137, 174].

Function

As mentioned above, the MTL is crucially involved in different cognitive processes. Due to its prominent role in various memory function, supported by numerous studies, many theoretical models have been put forward that aim to explain the involvement of the MTL regions in these functions. Besides the involvement of episodic memory, the MTL also plays a role in other processes, such as olfaction,

attention, spatial navigation and social cognition [85, 99, 110, 126, 138, 169, 173, 181, 233].

The MTL subregions have been shown to have specific and different functional involvement, enabling the complex processing required by the human memory system. Focusing first on the hippocampus, a functional difference (in contrast to the neuroanatomical demarcation into three parts) along the long axis of the hippocampus divides it into anterior versus posterior parts [227]. The anterior hippocampus is hypothesized to be involved in encoding of information [227] and recalling of scenes [324]. The posterior hippocampus has been hypothesized to be involved in retrieval [227] but also in spatial navigation and representation [260]. Additionally, the Cornu Ammonis fields and dentate gyrus are involved in pattern separation and completion [66, 238, 243]. The subiculum additionally relays processed information to other regions such as perirhinal and retrosplenial cortices [20, 272]. Note, however, that these functions are not completely segregated from each other [324].

Focusing on the cortical MTL regions, the entorhinal cortex processes object information (anterior entorhinal cortex) and spatial information (posterior entorhinal cortex) [179, 235]. It has been proposed that the perirhinal cortex functions to convert different aspects of memory processing (object representations to features that are object-associated) and by linking episodic and semantic memory [198]. Finally, the parahippocampal cortex is involved in both spatial or non-spatial contextual associations and processing [11].

Lastly, the different functions of the amygdala include fear and stress responses, appetite and thirst, motivational and reward behavior [269]. Note that amygdala subnuclei are involved differentially in these functions [269], but a detailed discussion goes beyond the scope of this thesis.

Vulnerability to pathology

The MTL is not by chance linked to the amnestic profile often seen in Alzheimer's disease. Hippocampal atrophy, for example, has repeatedly been described to occur in Alzheimer's disease dementia but also in mild cognitive impairment [98, 135, 166, 208]. The MTL is a hotspot for different neurodegenerative pathologies and different regions are hypothesized to be differentially vulnerable to various of these pathologies [95, 320].

Of primary interest and as mentioned before, the first cortical occurrence of tau neurofibrillary tangles (NFTs) is located in the MTL, specifically the medial portion of Brodmann area 35 (corresponding to the transentorhinal cortex) [35, 36]. NFTs accumulate in the projection (pyramidal) neurons of layer IIIu in Brodmann area 35 [69, 304], before spreading to the layer II cell islands (pre-α cell islands according

to Braak & Braak [34]) of the entorhinal cortex and the Cornu Ammonis 1 [34]. It is unclear why these regions exhibit this selective vulnerability to early NFT accumulation [177]. Not surprisingly, the trans- and entorhinal cortices have been shown to exhibit neurodegeneration in prodromal and preclinical stages of Alzheimer's disease [314, 315], which has been linked to decline in episodic memory [163] both in postmortem and in vivo studies [e.g., 116, 180, 197]. Additionally, the early occurrence of NFTs in the Cornu Ammonis has been shown to occur preferentially in anterior portions of the MTL first [2, 28, 92]. Given the hypothesis of prion-like spread of NFTs, the perforant path connecting the entorhinal cortex to the hippocampus, is a potential link between the spread from the entorhinal cortex to the hippocampal subfields [191].

NFT pathology alone does not fully explain the observed atrophy in the MTL [98, 166], and the co-occurrence of other neuropathologies in the MTL has, thus, been an important avenue of research. Such co-pathologies, as mentioned in prior sections are characterized by accumulation of TDP-43, α-synuclein, and Aβ, but also more diffuse effects on the brain by vascular pathology [157, 158, 185, 240, 252]. α-synuclein occurs, according to widely accepted staging schemes, early in the amygdala [19, 184], but has also been reported to target Brodmann areas 35 and 36 [e.g., 13, 145]. However, studies investigating α-synuclein accumulation in the context of Alzheimer's disease find limited associations with MTL subregional atrophy [93, 300]. While there are overlapping topographical occurrences of TDP-43 and NFT pathologies, TDP-43 pathology is assumed to first occur in the amygdala, followed by the hippocampal formation and then the middle frontal gyrus [208], which can be compared to the above shown Braak staging scheme of NFTs. TDP-43 was shown to affect the anterior hippocampus more, while atrophy in the posterior hippocampus appears to be more related to tau pathology [93]. Importantly, both pathologies occur in both regions even if it may be at different levels, potentially still affecting the regions [93].

To summarize, the MTL is vulnerable to early accumulation of tau pathology. Additionally, co-occurrence of other pathologies in the MTL additionally affect the structural integrity of the subregions and may affect some subregions more than others, within Alzheimer's disease.

Neuroimaging of Alzheimer's disease

As previously indicated, biomarkers are of increasing importance in the study of disease mechanisms, allowing for disease characterization beyond the sole reliance on cognitive symptom profiles. While postmortem assessments and fluid biomarkers are important, this thesis focuses on in vivo neuroimaging tools of aging and Alzheimer's disease: magnetic resonance imaging and positron-emission

tomography. These methods provide spatial information on neurodegeneration or hallmark pathologies in the brain.

Magnetic resonance imaging (MRI)

MRI is a tool that can non-invasively produce three-dimensional anatomical images of the brain [148]. Structural MRI is a key component of this thesis and is important when studying Alzheimer's disease. As mentioned above, atrophy of the hippocampus measured using MRI has been shown to be a key marker in Alzheimer's disease [e.g., 246]. This observation has prompted numerous studies investigating atrophy patterns and the association to cognitive functioning or Alzheimer's disease stages [e.g., 21, 117, 303, 323].

As the name indicates, an MRI scanner utilizes strong magnetic fields (at different strengths, such as 1.5, 3 or 7 Tesla). The magnets can be used to create signal from biological tissue, since they lead to alignment of protons in the magnetic field [148]. To generate and receive signal from the tissues, sequences of radiofrequency pulses, produced by coils in the scanner (radiofrequency coils), are applied, which temporarily displaces the protons from their alignment with the magnetic field as they precess (spin) [148]. Upon cessation of a radiofrequency pulse sequence, the protons undergo T1 and T2 relaxation, which is characterized by the release of energy at different rates [148]. The scanner measures these relaxation rates, which provide tissue-specific information used for image reconstruction [148]. Gradient fields are used to spatially encode the MR signal [148]. These are small differences in the magnetic fields at different strength across space, causing protons at different locations to precess at different frequencies and accumulate difference phases [148]. By analyzing these frequency and phase differences, the scanner can localize the signal and reconstruct an image [148].

While several different modalities are available, this thesis focuses on structural MRI, since this allows the investigation of grey matter atrophy by measuring volume or thickness of grey matter [254]. Two main structural MRI modalities are used: (i) T1-weighted MRI and (ii) T2-weighted MRI (Fig. 5). T1-weighted MRIs are the most commonly used structural MR images showing fatty tissue bright as the protons in this matter return back to their original orientation slower (longer relaxation time). Thus, CSF, which does not have fat is shown as black, grey matter as dark grey and white matter is shown as light grey, since the myelin that is protecting the fibers is fatty tissue [148]. T2-weighted MRI, on the other hand, shows CSF bright on the image, grey matter is shown as lighter grey, and white matter as dark grey [148]. Since internal details of the hippocampus can be visualized better with T2-weighted MRI, this is the preferred method to investigate hippocampal subregions [297].

These images can be processed in order to define regions of interest on the scans and measure them (e.g., as mentioned above volume or cortical thickness). This can

either be done by hand or by different available software packages [120]. Defining regions of interest by hand is particularly useful for small regions that can present as highly variable between individuals, since automated methods may not be able to capture and segment these differences properly [e.g., 5]. Available software that can be used today allows for the automated segmentation of the brain across individuals, allowing, for example, larger sample sizes to be handled. A typically used software to measure cortical thickness on MRI is FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) [249, 254], which parcellates the cortex according to an atlas of which some regions have been segmented based on postmortem investigations of a brain [89]. One drawback of FreeSurfer is, however, that the parcellations of the regions of interest are based probabilistically on a single individual [89]. Since the brain has a different morphology in each individual, this can lead to imprecise parcellations. Thus, other software based on a multi-atlas approach may provide more anatomically correct segmentations. A multi-atlas approach means that segmentation is done by registering MRI scans to an atlas, or library, of images segmented by experts. The algorithm finds the parcellation of segmentations that best matches a target MRI scan and creates a consensus segmentation giving highest weight to the images that most closely match the target image [289]. This has been proven to segment highly variable regions in an anatomically valid manner (e.g., Automated Segmentation of Hippocampal Subfields (ASHS) [315, 323]). In this thesis, T1- and T2-weighted structural MRI scans are used. FreeSurfer is utilized to extract thickness of neocortical regions and ASHS pipelines to extract volume and thickness of the medial temporal lobe subregions (Fig. 5).
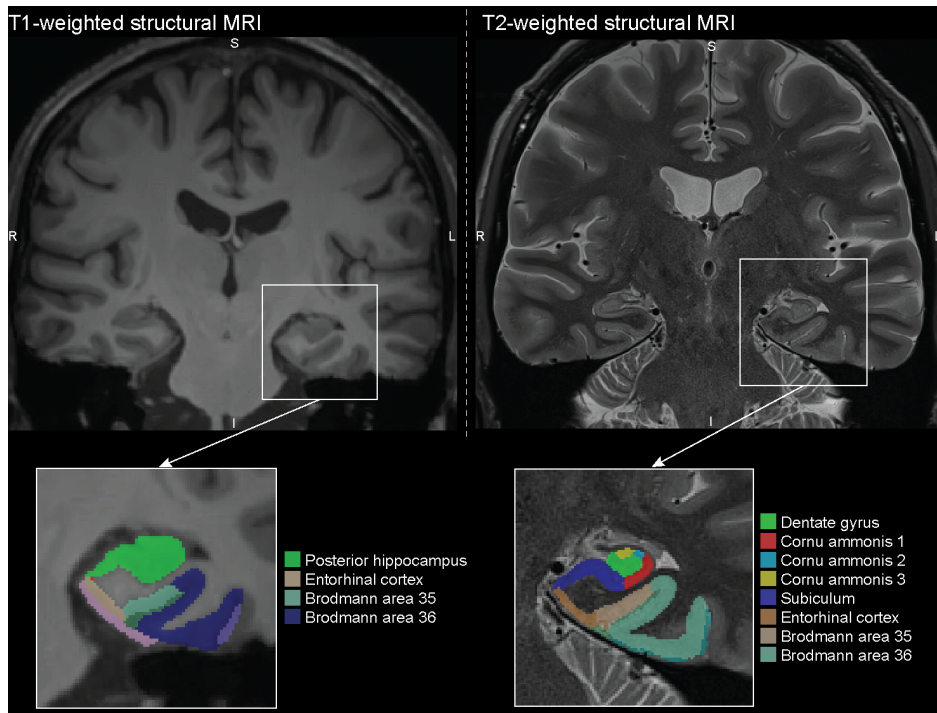
Fig. 5. Coronal T1- and T2-weighted structural MRI scans.
T1-weighted structural MRI (left) and T2-weighted structural MRI (right) and respective segmentations of the MTL using Automated Segmentation of Hippocampal Subfields. Images courtesy of Oskar Hansson. Abbreviations: I=inferior, L=left, R=right, S=superior.

Positron-emission tomography (PET)

PET allows the in vivo spatial investigation of where in the brain Aβ and NFTs are deposited by injecting a PET tracer. A PET tracer is composed of a radioisotope which emits positrons and is attached to a biological molecule (ligand) that binds to a given target (e.g., Aβ) [212]. When an emitted positron unites with a nearby electron in an annihilation event, two γ photons are emitted at 180 degree angles to each other, which are measured by the detectors of the PET scanner [212]. The scanner identifies which detectors register these γ photons, and by using this information the scanner determines the location of the annihilation event [212]. The resolution of a PET scan is limited by the short time interval between the release of the positron and the occurrence of the annihilation reaction [201].

One of the most commonly used analysis pipelines for PET involves the reconstruction of PET images which are overlaid on the subject-specific and segmented MR scan in order to extract the standardized uptake value ratios (SUVRs) of a given region of interest [248]. This is done by dividing the average uptake of the tracer in the region of interest with the average uptake in a reference

region. In the context of this thesis and the cohorts utilized, this standardization is done with reference regions unaffected in Alzheimer's disease. By doing this, a value of 1 SUVR can be interpreted as having a similar level of tracer uptake as the reference region, indicating little presence of the target protein in a given region [248]. A value larger than 1 indicates the presence of the target protein [248].

In 2004, the first Aβ-PET tracer (Pittsburgh Compound-B) became available [162] and several different Aβ-PET tracers are used today [162]. Some of these tracers were approved for the diagnostic workup of Alzheimer's disease by regulatory agencies ([^{18}F]-Flutemetamol, [^{18}F]-Florbetapir, [^{18}F]-Florbetaben) [200]. The available tracers were shown to bind to Aβ plaques, but they also show some off-target binding in the white matter [202, 278]. As mentioned previously, Aβ deposition follows a spatiotemporal pattern, which can be captured by Aβ-PET [104, 144, 186, 194, 279]. However, due to the widespread neocortical Aβ deposition in Alzheimer's disease, it is common to investigate global Aβ-PET measures, allowing the classification of individuals as Aβ-positive (Aβ+) and Aβ-negative (Aβ-) [52].

Since the mid-2010s, a number of PET tracers for tau pathology have become available [102]. The so-called first generation of tau-PET tracers, including flortaucipir ([^{18}F]-AV1451), showed uptake in line with expected patterns of tau pathology spread [49, 151, 253]. However, due to large off-target binding to choroid plexus in several regions, including the hippocampus [102], second-generation tau-PET tracers have been developed, such as [^{18}F]-RO948 [102, 259]. The tau-PET tracers bind to 3R and 4R tau and little uptake in non-AD neurodegenerative diseases has been shown [102, 172, 215], indicating its utility to investigate tau pathology in vivo.

Rationale and aims of the thesis

This thesis investigates the MTL in aging and Alzheimer's disease. The MTL's significance in this context stems from its vulnerability to various neuropathologies and its critical role in cognitive functioning, particularly memory. While the MTL has been studied in Alzheimer's disease, research has often relied on coarse neuroimaging measures of the MTL (e.g., total hippocampal volume). However, a granular study of MTL subregions is essential, given their differential vulnerability to neuropathologies and since they subserve different aspects of cognition.

Development of reliable in vivo methods for measuring MTL changes are essential in this context. The MTL's anatomical heterogeneity complicates the subregional study, necessitating further methodological advancements. Imaging MTL subregions offers enhanced insights into disease mechanisms and could potentially serve as biomarkers in clinical practice for early Alzheimer's disease (co-)pathology or secondary endpoints in clinical trials. As clinical trials target earlier diseases stages, identifying suitable participants who could benefit from potential treatments becomes paramount. This requires the ability to detect subtle changes in early regions and a comprehensive understanding of granular changes in the MTL in relation to cognition across the Alzheimer's disease continuum, and in different Alzheimer's disease presentations.

Based on this rationale, the two overarching objectives of this thesis are to (i) contribute to the methodological advancements of MRI-based measures of MTL subregions and (ii) characterize MTL subregional atrophy and its contributions to cognitive decline in aging and Alzheimer's disease.

Based on this rationale, the aims of this PhD project are the following (Fig. 6):

I. To develop refined and sensitive methods for measuring MTL subregions. This work will contribute to this by enhancing the knowledge of the anatomical organization of cortical MTL subregions and developing a segmentation protocol for the amygdala (***papers I-II***).

II. To characterize MTL and neocortical changes related to NFTs in aging populations in the absence of significant Aβ pathology (***paper III***). This will provide more insights in the relevance and effects of NFT pathology in aging.

III. To investigate region-specific atrophy in the MTL and neocortical regions as a pathway of tau-induced impairments in decline of different cognitive subdomains (***paper IV***).

IV. To enhance our understanding of distinct Alzheimer's disease presentations by elucidating potential differences in MTL atrophy patterns for sporadic amnestic early-onset and late-onset Alzheimer's disease (***paper II – part 2***).

V. To review the relative contributions of NFT and TDP-43 pathology to MTL atrophy (***paper V***).
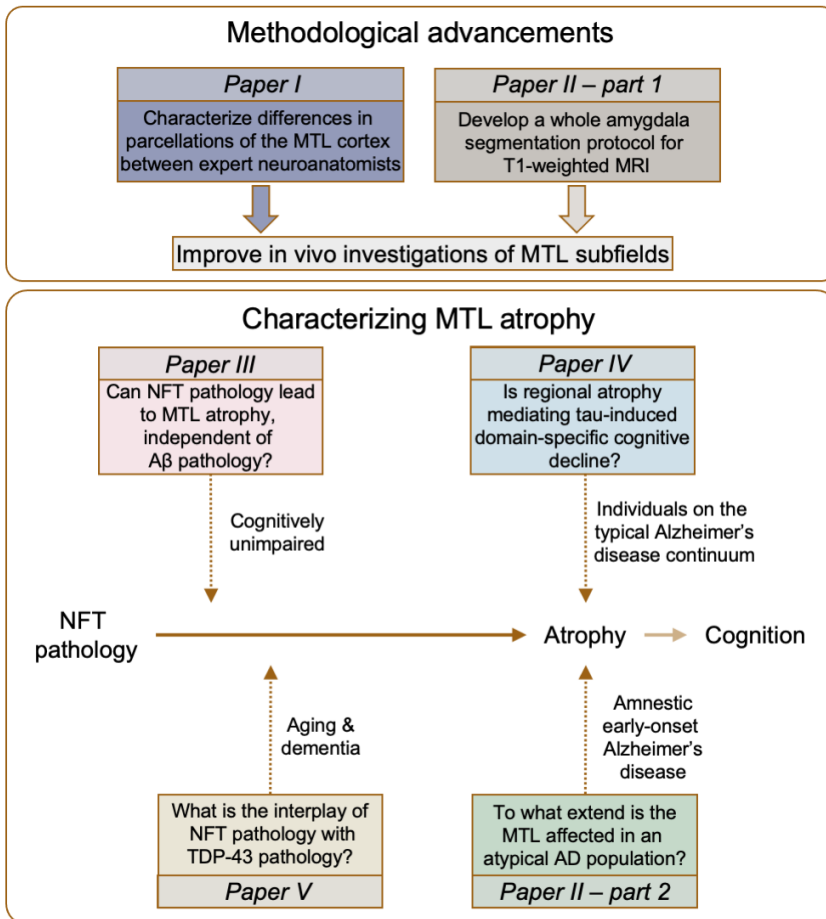
Fig. 6. Overview of papers, research questions, and studied populations.
This thesis contributes to two overarching aims: (i) methodological advancements of structural MTL measurements, and (ii) characterizing MTL subregional atrophy and its contributions to cognitive decline in aging and Alzheimer's disease. The figure gives an overview of the main research question per paper within these two aims. Study populations are indicated on the arrows and main research question in respective boxes. Abbreviations: Aβ=amyloid-beta; AD=Alzheimer's disease; MTL=medial temporal lobe; NFT=neurofibrillary tangle; TDP-43= Transactive response DNA-binding protein 43 kDa.

Methods

An overview of the methods relevant for this thesis is shown below (Fig. 7).
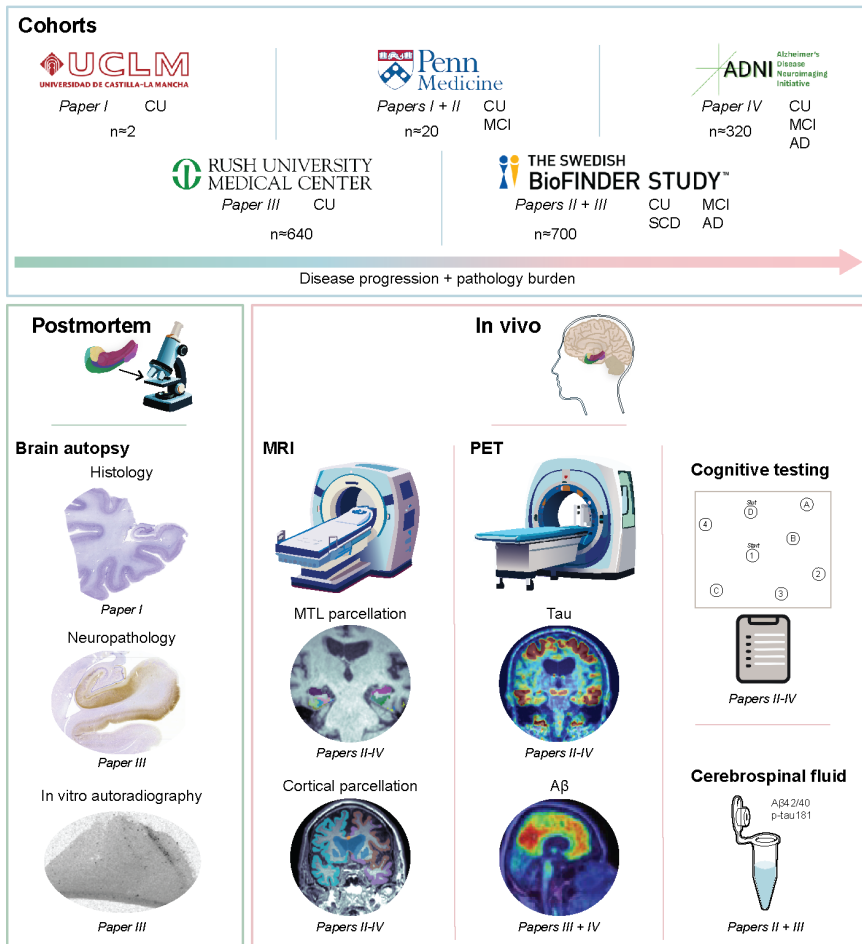
Fig. 7. Overview of the utilized cohorts and different methods employed in this thesis.
On the top panel, the different utilized cohorts are shown, indicating for which papers they were used, the sample size, and which groups were included. On the bottom panels the postmortem (left) and in vivo (right) methods are summarized. Abbreviations: Aβ=amyloid-beta; AD=Alzheimer's disease; CU=cognitively unimpaired; MCI=mild cognitive impairment; n=sample size; SCD=subjective cognitive decline; tau=tau-PET.

During the preparation of this thesis, the AI language model Gemini was used solely to improve writing style and check grammar. The tool was never asked to generate new text. Additionally, the tool was prompted to propose several options for a given sentence and text was never copied. Instead, different options provided by the tool were reviewed and used to improve the writing. Thus, it was used in the same way as commonly used academic proofreading services. The author takes full responsibility for the content of the publication.

Study cohorts

The thesis utilizes the data of six different cohorts. Due to the different designs and aims of the studies, different data modalities were required. *Paper I* used data from the University of Pennsylvania and the University of Castilla-La Mancha. The primary source of data for *papers II* and *III* is the Swedish BioFINDER-2 study. *Paper II* additionally included MRI scans from the Penn Memory Center, University of Philadelphia, for method development. To validate results of *paper III* additional data from the Rush Alzheimer's Disease Center cohort studies was utilized. The data used in *Paper IV* comes from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Since *paper V* is a literature review, no data was included in this project.

Postmortem cases of the University of Pennsylvania and the University of Castilla-La Mancha

The Human Neuroanatomy Laboratory at the University of Castilla-La Mancha in Albacete (UCLM), Spain and the Center for Neurodegenerative Disease Research (CNDR) at University of Pennsylvania (UPenn), USA, are collaborating to build a bank of postmortem and in vivo MRI scans, coupled with histology and neuropathology. The aim of this is to develop computational methods for understanding the consequences of diseases or interventions over time. In this thesis, three subjects of this cohort were selected, and their data were used in *paper I*.

BioFINDER-2

The Swedish BioFINDER-2 study (NCT03174938, https://biofinder.se/two/) features a wide range of biomarker and cognitive data, making it one of the largest multi-modal Alzheimer's disease studies worldwide. The study is a longitudinal observational cohort study including healthy middle aged, healthy elderly, SCD, MCI, and dementia participants [217]. The aims of the study include developing methods for improved diagnosis and prognosis of dementia disorders including

understanding heterogeneity and temporal evolution of dementia disorders, as well as developing biomarkers and imaging techniques. The study was launched in 2017, has enrolled more than 2500 participants, and is currently ongoing. Participants are enrolled consecutively at the Skåne University Hospital (memory and neurology clinics) and the Ängelholm memory clinic. Data of this cohort were used in *papers II* and *III*.

Penn Memory Center atlas set

This set of MRI scans consists of 15 cognitively normal older controls and 14 patients with amnestic MCI. Recruitment occurred at the Penn Memory Center at the University of Pennsylvania. This atlas set is used to the Automated Segmentations of Hippocampal Subfields packages [313, 315, 316, 323]. This atlas set was utilized for *paper II*.

Rush Alzheimer's Disease Center cohort studies

The Rush Alzheimer's Disease Center (RADC; https://www.rushu.rush.edu/research-rush-university/departmental-research/rush-alzheimers-disease-center), is funded by the National Institute on Aging and has several different ongoing cohort studies. Here, we utilized data from Religious Orders Study, Rush Memory and Aging Project, Minority Aging Research Study, and African American Clinical Core [15, 23, 251]. All cohorts are longitudinal, epidemiologic cohort studies enrolling participants from healthy aging to Alzheimer's disease. These studies involve a postmortem neuropathological evaluation of all participants that agree to brain donation. The studies include a variety of data and biospecimens, aiming to gather knowledge to treat and prevent dementia. Data of this cohort were used in *paper III*.

Alzheimer's Disease Neuroimaging Initiative

The Alzheimer's Disease Neuroimaging Initiative (https://adni.loni.usc.edu/), ADNI in short, is a multi-center, longitudinal observational study. The design of the study aims to develop and validate biomarkers (clinical, genetic, biochemical, imaging) for detecting and improving diagnostics of Alzheimer's disease, as well as for informing Alzheimer's disease clinical trial. Additionally, they provide data to scientists through a data-access policy enabling open data sharing. The study was designed to reflect a real-world clinical trial cohort and includes over 2000 individuals who are cognitively unimpaired or have MCI or dementia. The ADNI was initiated in 2004 and is currently ongoing, having adjusted the exact study design to reflect and incorporate new methods and measures, resulting in different study phases. Data of phases two and three were used in *paper IV*.

Postmortem methods

Histology

Serial histology sections from the three postmortem cases of UCLM and UPenn were only used in *paper I*. In order to obtain these sections of the cases, fixation of the brains was performed using either 4% paraformaldehyde in 0.1 M phosphate buffer (UCLM) or 10% neutral buffered formalin (UPenn).

After fixation, one hemisphere was used for diagnostic neuropathology, while the other hemisphere was dissected to obtain the full temporal lobe. The temporal lobe was cut coronally into four blocks (20mm thick) after which the blocks were frozen and 50μm thick serial sections were cut. The obtained sections were mounted and Nissl-stained with thionin.

The sections were then mounted on glass slides and scanned and uploaded on a digital platform. 15-16 digitized slices (5mm apart) of the Nissl-stained sections per case were selected and annotated by four expert neuroanatomists. The neuroanatomists performed annotations of four MTL cortical subregions (i) entorhinal cortex, (ii) Brodmann area 35, (iii) Brodmann area 36, and (iv) parahippocampal cortex. For more details see [308, 321].

Neuropathology

Neuropathological assessment of the RADC cohort was used to validate our in vivo findings of *paper III* and follows the guidelines for neuropathological assessment of the National Institute on Aging [125].

Aβ proteinopathy load was measured based on the mean square root transformation of the percentage area of cortex occupied in eight brain regions. Immunohistochemistry was done with monoclonal antibodies (1-40 and 1-42 Aβ; 4G8 (1:9000; Covance Labs), 6F/3D (1:50; Dako North America Inc.) and 10D5 (1:600; Elan Pharmaceuticals)).

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) recommendations [196] for assessing Aβ status in a semi-quantitative estimate of neuritic plaque density was done using modified Bielschowsky-stained sections. Bielschowsky silver staining in five regions were used to determine Braak stages [35, 36]. Burden of overall tau NFT pathology was calculated using the square root of AT8 immunohistochemistry staining scores. This antibody is specific to phosphorylated tau. AT8 staining is thought to be able to immunostain pre-tangles and mature tangles, while the Bielschowsky silver staining has been shown to visualize neuropil threads, mature tangles and ghost tangles [199].

Given that this is an established cohort, all details are provided by the RADC [15, 23, 24, 251].

Autoradiography

Autoradiography is used to investigate the presence and/or distribution of a targeted protein in tissue by binding a radioligand to the target [101]. In ***paper III*** [309], we aimed to validate the utilized [^{18}F]-RO948-PET tracer for use in PART. To this end, and in collaboration with Roche Pharmaceutical Research and Early Development (Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Switzerland), autoradiography was performed in one PART case, as defined by no Aβ plaque deposition (CERAD neuritic plaque score = 0, Thal phase = 0) but tau tangle pathology rated as Braak stage IV.

Sections of brain tissue from this case were incubated at room temperature with the radioligand [^{3}H]-RO948 (10nM) in Tris-HCl buffer (50 mM, pH: 7.4). The same solution was used to wash the section thrice and finally dried, after which the section was scanned (25μm/pixel). Finally, the sections were assessed for co-localization with tau pathology (AT8 staining) in order to establish if the tracer is binding to tau aggregates.

Neuropathological assessment was additionally performed by collaborators for a PART case in order to diagnose PART and compare the immunostaining of AT8 with autoradiography results.

In vivo neuroimaging methods

Structural MRI

While structural 3T MRI was employed for ***papers II-IV***, differences in imaging protocols exist for the different study cohorts. In the BioFINDER-2 cohort utilized in ***papers II*** and ***III***, structural T1- and T2-weighted MRI scans were acquired using a Siemens MAGENTOM Prisma 3T scanner. In the ADNI cohort utilized in ***paper IV***, structural T1-weighted MRI scans were acquired using several different scanners, since the ADNI is a multi-center cohort. All scanners are 3T scanners either from General Electric (GE) Healthcare, Philips Medical Systems, or Siemens Medical Solutions. All MR images were reconstructed and processed before applying automated segmentation methods.

T1-weighted magnetic resonance imaging protocols

In the BioFINDER-2 cohort, utilized in ***papers II*** and ***III***, magnetization prepared-rapid gradient echo (MPRAGE) sequence with a resolution of 1mm isotropic was used (TR = 1900 ms, TE = 2.54 ms, flip-angle = 9°). Images are reconstructed and processed before applying segmentation methods.

In the ADNI cohort, utilized in ***paper IV***, MPRAGE sequences with a resolution of 1.0x1.0x1.2 mm were acquired. The exact protocols of the ADNI study are dependent on the study phase and are available under https://adni.loni.usc.edu/data-samples/adni-data/neuroimaging/mri/mri-scanner-protocols/.

T2-weighted magnetic resonance imaging protocols

Data from T2-weighted sequences were only used in ***papers II*** and ***III*** employing data from BioFINDER-2. These scans were acquired using a turbo spin echo sequence with an in-plane resolution of 0.4 mm^2 (slice thickness = 2 mm, TR = 8240 ms, TE = 52 ms, flip-angle = 150°).

In ***paper II***, information from T2-weighted Fluid attenuated inversion recovery (FLAIR) images was additionally used (1mm isotropic, TR = 5000 ms, TE = 393 ms, TA = 4.37 min).

Automated Segmentations of Hippocampal Subfields

For ***papers II-IV***, the Automated Segmentation of Hippocampal Subfields (ASHS) packages were used to obtain measures of hippocampal subfields. Different packages exist for T1- and T2-weighted MR images. Volumes of hippocampal subfields are extracted from T2-weighted ASHS package and routinely corrected for intracranial volume (ICV, volume-to-intracranial volume fraction). For MTL cortical regions, median thickness is measured using the T1-weighted MRI ASHS package. Median thickness is commonly chosen since it is less affected by segmentation errors than mean thickness. These packages were used for both the BioFINDER-2 and the ADNI data. It was previously shown that the ratio of anterior hippocampus and parahippocampal cortex, could be used as an MRI-based proxy of TDP-43 pathology [93]. Thus, this ratio was used in ***paper II***.

As part of ***paper II***, the T1-weighted MRI ASHS package was extended to include a segmentation of the whole amygdala using a newly developed segmentation protocol [310].

As gold-standard practice, automated segmentations are checked for their quality in order to ensure high quality of the segmentations [45]. These quality controls have been performed in both the BioFINDER-2 cohort (performed by members of the group at Lund University, including myself) and the ADNI data (performed by members of the Penn Image Computing and Science Laboratory at UPenn).

Parcellations of the neocortex

Using the T1-weighted MR images, cortical thickness and total intracranial volume (ICV) were extracted for papers ***II-IV***. FreeSurfer (version 6.0, https://surfer.nmr.mgh.harvard.edu/) was applied in the BioFINDER-2 cohort using the Desikan-Killiany atlas in order to obtain mean thickness.

For the ADNI cohort, total ICV was also extracted using FreeSurfer. Cortical thickness was extracted using the DiReCT method [61, 161, 281, 289].

The parcellated regions of interest (ROIs) were used to generate mean cortical thickness estimates averaged across hemispheres for all papers.

White matter hyperintensity measures

Using FreeSurfer version 7.2, Sequence Adaptive Multimodal SEGmentation, or SAMSEG, was used to segment white matter hyperintensity (WMH) volumes for the whole brain from the T2-weighted FLAIR images. As done for hippocampal volumes, the WMH volumes were corrected for ICV in the same manner.

PET

Partial volume correction (PVC) is a method to adjust the images for partial volume effects that can arise, typically in smaller ROIs where off-target binding can occur [241]. This has been shown to be beneficial in improving signal for these regions when using cross-sectional but not longitudinal data [56].

Tau-PET

In all studies including in vivo data (***papers II-IV***), tau-PET was employed as a method to measure tau pathology in the brain. Two different tracers were used: $[^{18}F]$-RO948 and $[^{18}F]$-Flortaucipir. For both tau-PET tracers, ~370 MBq were injected, and the scan was performed 70-90 min post-injection for BioFINDER-2 and 75 minutes post-injection for the ADNI. Using the inferior cerebellar region as reference, SUVRs were calculated for both tracers and PVC was performed using the geometric transfer matrix method [241].

In the BioFINDER-2 cohort, the $[^{18}F]$-RO948 tracer was used. In ***paper II***, tau-PET uptake was measured in an MTL composite region (entorhinal cortex and Brodmann area 35) and in the amygdala. Additionally, neocortical regional composite measures were additionally calculated based on [171], namely the lateral temporal, parietal, frontal and occipital/motor composite regions. In ***paper III,*** the same MTL composite regions were calculated and additionally tau-PET SUVR in inferior temporal, superior frontal, orbitofrontal, anterior cingulate, posterior cingulate/precuneus, supramarginal and lateral occipital regions.

For the study using ADNI data (***paper IV***), tau-PET data was collected using the [^{18}F]-Flortaucipir tracer. Again, the SUVR for the MTL composite region (entorhinal cortex and Brodmann area 35) was calculated and additionally a neocortical composite region combining angular, inferior temporal, middle frontal, superior frontal, supramarginal gyri, superior parietal lobule, precuneus, and temporal pole.

Aβ-PET

In papers ***III and IV*** Aβ-PET was used to measure Aβ pathology in vivo. Different tracers were employed in different cohorts. Yet, for all papers, the whole cerebellum was used as a reference region.

In ***paper III***, SUVRs after PVC correction were calculated from [^{18}F]-Flutemetamol uptake for an "early Aβ" neocortical composite region including specific frontal, parietal and temporal regions [218], as well as global uptake combining all frontal, parietal and temporal regions [214]. The global uptake was utilized to determine Aβ status. The participants were scanned 90–110 min post injection of ~185 MBq of the tracer.

In ***paper IV***, using ADNI data, Aβ-PET was measured either with [^{18}F]-Florbetaben (~370 MBq, 90 min post-injection) or [^{18}F]-Florbetapir (~300 MBq, 50 min post-injection), depending on the phase of the study. Global Aβ-PET [168] was calculated also for this study, again using frontal, parietal and temporal regions, in order to determine Aβ status.

Cognitive testing

In three papers (***II-IV***), cognitive testing was used to assess the cognitive function of study participants. Table 2 provides an overview of the tests employed in each study.

The Mini-Mental State Examination (MMSE) is a tool to screen for mental impairment [94]. The total score on this test is the number of correct answers, leading to a maximum score of 30 points. While this tool has been shown to be able to identify cognitive impairment, it does not have high diagnostic specificity [270]. The Preclinical Alzheimer Cognitive Composite (PACC) is a composite measure of cognitive functioning designed to be sensitive to preclinical Alzheimer's disease (Aβ-positive CU individuals) [72]. Based on theoretical and data-driven knowledge, this composite includes learning and recall, executive function and global cognition measures. In ***paper III***, the modified PACC was utilized since slightly different cognitive measures were available in BioFINDER-2 compared to the original PACC [222]. As shown in Table 2, the MMSE, ADAS-Cog delayed word list recall

(double-weighted), the Symbol Digit Modalities Test, and category fluency were used to calculate the modified PACC.

The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), developed to estimate cognitive impairment in Alzheimer's disease, consists of different subtests [53, 100, 224]. For *papers II-IV*, the delayed word list recall measure was utilized as a measure of episodic memory. For *paper IV*, also the Auditory Verbal Learning Test (AVLT) was used to estimate different episodic memory subfunctions [237, 282]. Similarly to the ADAS-Cog, this is also a 15-word list learning task, which over several trials measures immediate, late and delayed recall, as well as recognition.

The Boston Naming Test (BNT) was used in *paper II*, to investigate visual naming abilities of objects. Verbal fluency, commonly used to assess production of words, can be evaluated for different conditions [270]. Semantic fluency (*papers II-IV*) is commonly assessed using categories such as animals and vegetables, while phonemic fluency is commonly assessed using the letters F, S, or A [270]. The Trail-Making Test (*papers II* and *IV*) is a test of executive function, consisting of two subtests (A and B), where either only numbers or number and letters in a alternating manner should be connected as fast as possible [236, 270]. Part A primarily assesses attention and speed, while these function in addition to mental flexibility are assessed in part B [236, 270]. The Symbol Digit Modalities Test (*paper II*) measures divided attention, visual scanning and motor speed by asking patients to fill in numbers connected to different symbols as fast as possible [258, 270]. Finally, the Visual Object and Space Perception Battery (VOSP, *paper II*) includes a subtest entitled "Cube analysis" which assesses visuoconstructive skills by asking how many cubes are shown, outlined on a card [291].

In *paper IV*, we additionally employed an approach commonly used for the Trail-Making Test also for other cognitive measures by adjusting cognitive subdomains in order to obtain purer measures of function. In short, each cognitive subdomain was adjusted for another relevant cognitive domain. Late recall was adjusted for immediate recall to account for attention. Recognition was adjusted for delayed recall to obtain a measure of familiarity but not recollection. Category fluency was adjusted for letter fluency and the Trail-Making-Test B was adjusted for the A version. Immediate recall was not adjusted since it is not assumed to be affected by other domains. Additionally, delayed recall was not adjusted as it is not assumed to be affected by attention. More information about this can be found in the manuscript in the appendix.

Table 2. Cognitive tests utilized in this thesis per paper.
Note: x indicates that the test was directly used as outcome measure, *(x)* indicates that the test was used to calculate a composite measure and [x] if it was used for correction of another measure, not as an outcome measure.

Cognitive test	Function	Paper II	Paper III	Paper IV
Mini-Mental State Examination	Screening tool	x	*(x)*	
Modified Preclinical Alzheimer Cognitive Composite	Composite measure		x	
ADAS-Cog delayed word list recall	Episodic memory	x	x	x
Auditory Verbal Learning Test (all trials)	Episodic memory			x
Boston Naming Test	Visual naming ability	x		
Category fluency	Semantic fluency	x	*(x)*	x
Letter fluency	Phonemic fluency			*[x]*
Trail-Making Test	Attention, speed, mental flexibility	x		x
Symbol Digit Modalities Test	Divided attention, visual scanning, tracking, motor speed	x	*(x)*	
Visual Object and Space Perception Battery - Cube	Visuoconstructive skills	x		

Cerebrospinal fluid biomarkers

In *papers II* and *III*, the CSF was collected and analyzed for the included BioFINDER-2 participants. In this study, all handling of CSF followed a standardized protocol [112, 141]. Samples were centrifuged following the collection and stored at -80 °C until analysis.

For the purposes of the studies in this thesis, the CSF Aβ42/Aβ40 ratio was utilized to determine Aβ status using the Roche Elecsys platform (Roche Diagnostics International Ltd.) [114]. For *paper II*, some participants' Aβ status was determined using also the Lumipulse G (Fujirebio) or Meso-Scale Discovery instruments due to missingness on the primary assay. A cut-off was applied based on Gaussian mixture modelling, previously established for the BioFINDER-2 cohort (Elecsys: 0.080; Lumipulse G: 0.072; MSD: 0.077).

In *paper III*, CSF p-tau181 was measured using the automated electrochemiluminescence immunoassay (cobase 601, Roche Diagnostics International Ltd.).

Study design

Paper I

The Nissl-stained histology slices from UCLM and UPenn were annotated by four expert neuroanatomists. The parcellations of the neuroanatomists were compared in terms of border placement but also for differences in terminology and definitions for MTL cortex subregions that the neuroanatomists utilized to perform the annotations. The donors were between 66 and >90 years old (in order to increase privacy, ages above 90 are not allowed to be disclosed in the U.S. where this data comes from) and were chosen to represent a wide age range, both hemispheres, differential sulcal patterns, and cases with and without neurogenerative disorders.

Paper II

This paper includes two projects of the thesis: (i) to develop a segmentation protocol for T1-weighted MRI for the whole amygdala and (ii) to investigate MTL subregion atrophy patterns in amnestic early-onset Alzheimer's disease. In the results and discussion sections, these will be referred to as ***paper II – part 1*** and ***paper II – part 2***.

For the first part of the project, included in the supplements of the published article, a segmentation protocol for the whole amygdala on T1-weighted MRI was developed. Not all borders of the amygdala can be clearly identified on MRI, thus, some geometric rules had to be determined, with the help of the above-mentioned atlases. The protocol development was informed by human brain atlases [68, 182] and segmentations were done using ITK-SNAP [319, 322]. The tracing of the amygdala was done on the coronal plane. Sagittal and axial planes were used to inspect and edit the segmentations. Intra-rater reliability was assessed by segmenting the same 15 cases twice, first, at baseline and, second, after three weeks. Finally, this protocol was implemented in the T1-weighted ASHS package.

For the clinical part of the study, in total 534 individuals (cognitively unimpaired, MCI or Alzheimer's disease) from BioFINDER-2 were included. Amnestic early-onset Alzheimer's disease subjects (n = 41) had (i) MCI (MMSE$\geq$24) or Alzheimer's disease (MMSE$\geq$20), were (ii) 50-65 years of age, (iii) CSF Aβ42/Aβ40 ratio and tau-PET positive, and (iv) below age- and education-based norms on the ADAS-cog delayed word list recall [271]. As comparison groups, amnestic late-onset Alzheimer's disease (n = 154, >70 years) and healthy controls (young and old) were included. Comparisons were done for MTL subfield volumes/thickness. Exploratory comparisons were done for Alzheimer's disease pathologies (CSF Aβ42/Aβ40, MTL and amygdala tau-PET), co-pathologies (WMH, MR-based proxy of TDP-43 pathology), and for cognitive performance, as well as for the association between MTL measures and cognitive tests (listed in Table 2).

Paper III

The study population consisted of cognitively unimpaired individuals from BioFINDER-2 (n = 545) and as validation cohort, cognitively unimpaired RADC participants (n = 639). We investigated (i) the associations between age and tau pathology in the whole samples and in the Aβ-negative individuals, (ii) the associations between tau pathology and volume/thickness in MTL and neocortical regions, and (iii) the associations between tau pathology and cognition.

As part of validating the [18F]-RO948-PET tracer in the context of cognitively unimpaired cases, the autoradiography in a brain section of a PART case was performed.

Paper IV

Utilizing data from the ADNI, 319 individuals on the Alzheimer's disease spectrum (Aβ-positive cognitively unimpaired, MCI, and Alzheimer's disease) were included in this study. MTL and neocortical volume/thickness were measured and tau quantified using [18F]-Flortaucipir. Six cognitive subdomains were investigated (listed in Table 2) and adjusted to obtain purer measures, as described above.

Paper V

This paper is a narrative review aiming to increase the understanding of the interplay between tau and TDP-43 pathology and their effects on MTL structure. A comprehensive literature review was performed, and information was integrated in order to evaluate the relative contributions of tau and TDP-43 to MTL atrophy and to generate directions for future research.

Statistical analyses

All statistical analyses were performed in R [230]. P-values were controlled for the false discovery rate (FDR, Benjamini-Hochberg procedure) and considered statistically significant at $p < 0.05$.

Paper I

Due to the descriptive nature of the work and the small sample size, no statistical analyses were performed.

Paper II – part 1

For the protocol development, reliability analyses were performed. First, interrater reliability was assessed using intraclass correlation coefficient and dice similarity index. Second, after implementation of the protocol in ASHS, a cross-validation of

the manual with the automated segmentations was performed and a dice similarity index reported.

Paper III

For this project, Pearson partial correlations were calculated to assess the associations between (i) age and tau-PET, (ii) age and thickness/volume, and (iii) tau-PET and thickness/volume, including sex and Aβ-PET as covariates. Similar associations were investigated using Spearman rank correlations for the RADC postmortem data. All analyses were done in the full cognitively unimpaired cohort and in the subsample of Aβ-negative individuals. Additionally, mediation models were created to investigate the mediating effects of tau-PET on the age-thickness association when adjusting for Aβ-PET. Finally, similar analyses were done for global cognition and delayed word list recall.

Paper IV

Associations between tau-PET, thickness and cognitive subdomains were assessed, including age, sex, education and the respective cognitive measure mentioned above as covariates, using linear regression models. This was done to select which predictors were to be further investigated. To understand which regional thickness/volume contributed to explaining the association between tau-PET and cognitive subdomains, mediation models were created. These models were performed for each cognitive subdomain, with MTL subregion measures investigated as mediator for MTL tau-PET and cognitive subdomain, and regional neocortical thickness for neocortical tau-PET and cognitive subdomain associations. In a final step, complex mediation models included all significant mediators for a given cognitive subdomain. The models included age, sex, education, and the respective cognitive measure as covariates.

Paper II – part 2

For the clinical study, comparisons between groups were investigated using one-way analyses of covariance (ANCOVA), with sex added as covariate, and with post-hoc Tukey's HSD Test. Group comparisons were done for young controls versus early-onset Alzheimer's disease, older controls versus late-onset Alzheimer's disease, and for the two Alzheimer's disease groups. Comparisons focused on differences in MTL structure, biomarkers of Alzheimer's disease and co-pathologies, and cognitive performance. Additionally, associations between continuous variables were investigated using linear regression models.

Paper V

This paper is a narrative review. Thus, no statistical analyses were performed.

Main results

In the following section, the main results of each paper are described. For all details concerning methodology and additional results, including sensitivity analyses, please see the individual papers in the appendix of this thesis.

Paper I

This paper centered around the observation that neuroanatomical schools employ different cytoarchitectonic definitions of MTL subregions [308]. This study investigated to what extent delineations of subregions overlap between these schools. This is not only important for the field of neuroanatomy, but also of relevance for neuroimaging research as neuroanatomical atlases are crucial for the development of segmentation methods for in vivo MRI. Thus, we provide an overview of cytoarchitectonic definitions of the entorhinal and parahippocampal cortices and adjacent Brodmann areas (BA) 35 and 36 by four neuroanatomists, aiming to identify reasons for overlapping and diverging delineations (see Table 3) [308].

Table 3. Key features of the MTL cortex subregions.
Note: [1] Disagreement in definitions is indicated by "or". [2] The exact anatomical location may vary, e.g., due to heterogeneity in collateral sulcus [69]. [3] See Table 4 of the paper for details. [4] Some neuroanatomists refer to only the external cell-free layer as lamina dissecans. [5] Does not apply to the isocortex of the posterior PHC [267]. Abbreviations: BA=Brodmann area; CS=collateral sulcus; ERC=entorhinal cortex; PHC=parahippocampal cortex.

	ERC	Perirhinal	Ectorhinal	PHC
Brodmann area	28, 34	35	36	-
Cortex type[1]	Periallocortex	Periallocortex and/or proisocortex	Proisocortex or isocortex	Periallocortex, proisocortex, and isocortex[5]
Location[2]	Crown of the parahippocampal and ambient gyri	Medial and/or lateral bank of the CS	CS and/or crown of the fusiform gyrus	Crown of the parahippocampal gyrus, medial bank of the CS
Seminal feature	- layer II cell islands - *lamina dissecans*[4] - layer of large	- columnar organization of layers II and III - no *lamina dissecans*, but	- increasing granularity in layer IV - gradual transition of	- wide internal layers - agranular (medial) to granular (lateral)

	pyramidal cells adjacent to one or two *laminae dissecans*[4]	agranular, and/or dysgranular layer IV	layer VI to white matter	layer IV - gradual transition between layers V and VI
Agreement[3]	**High**	**Intermediate to high**	**Intermediate**	**Low to intermediate**

Qualitative analysis of the annotations showed higher agreement in the definitions of the entorhinal cortex and BA35, while BA36 and the parahippocampal cortex exhibited less overlap (Fig. 8).
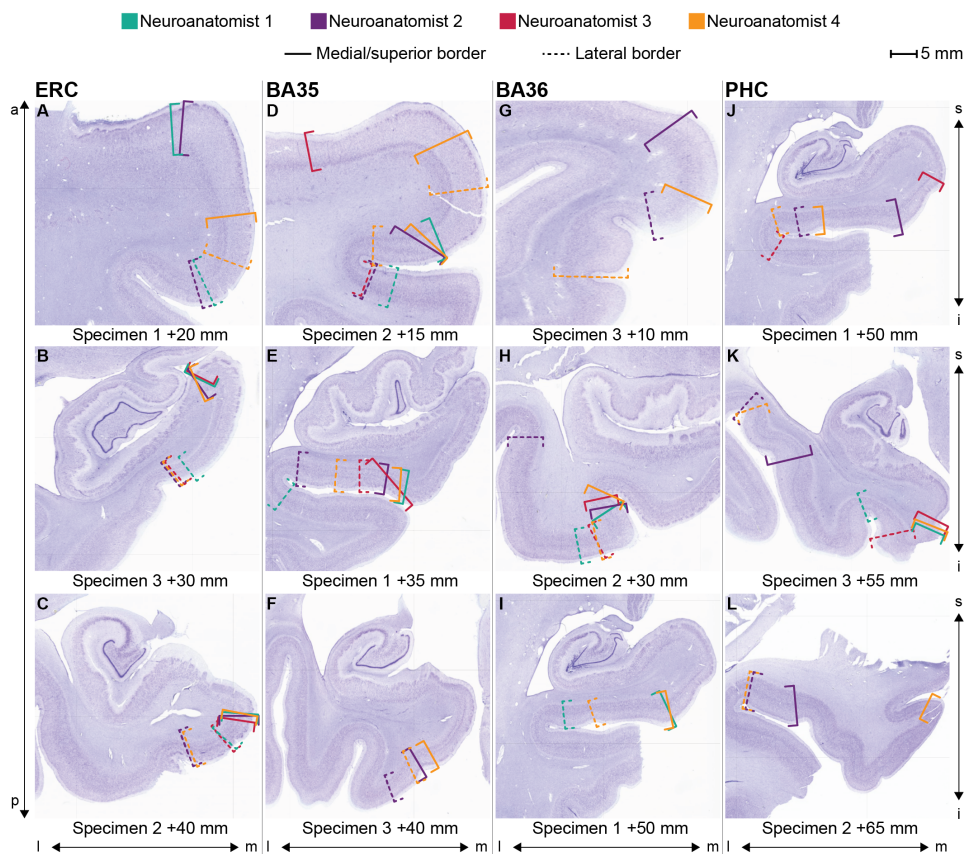

Fig. 8. Overview of overlap and disagreement for example MTL cortex delineations.
Anterior, mid-section, and posterior parts of the four MTL cortex subregions are displayed. Millimeters=distance from temporal pole. Abbreviations: a=anterior; BA=Brodmann area; ERC=entorhinal cortex; i=inferior; l=lateral; m=medial; p=posterior; PHC=parahippocampal cortex; s=superior. Figure reprinted from [308] (CC BY).

The degree of overlap of cytoarchitectonic definitions or lack thereof was partially reflected in the neuroanatomists' (dis-)agreement on the performed delineations

(Fig. 9). Lower agreement in annotations was observed in transitional zones where cytoarchitectonic features are expressed saliently or due to differences in definitions (Fig. 9). It is important to be aware that even though seemingly clear distinctions can be made between the different MTL subregions, no concrete or definite border can be placed. Instead, the characteristic features of one region gradually transition into the features of the adjacent region, making definite border placement challenging [127].
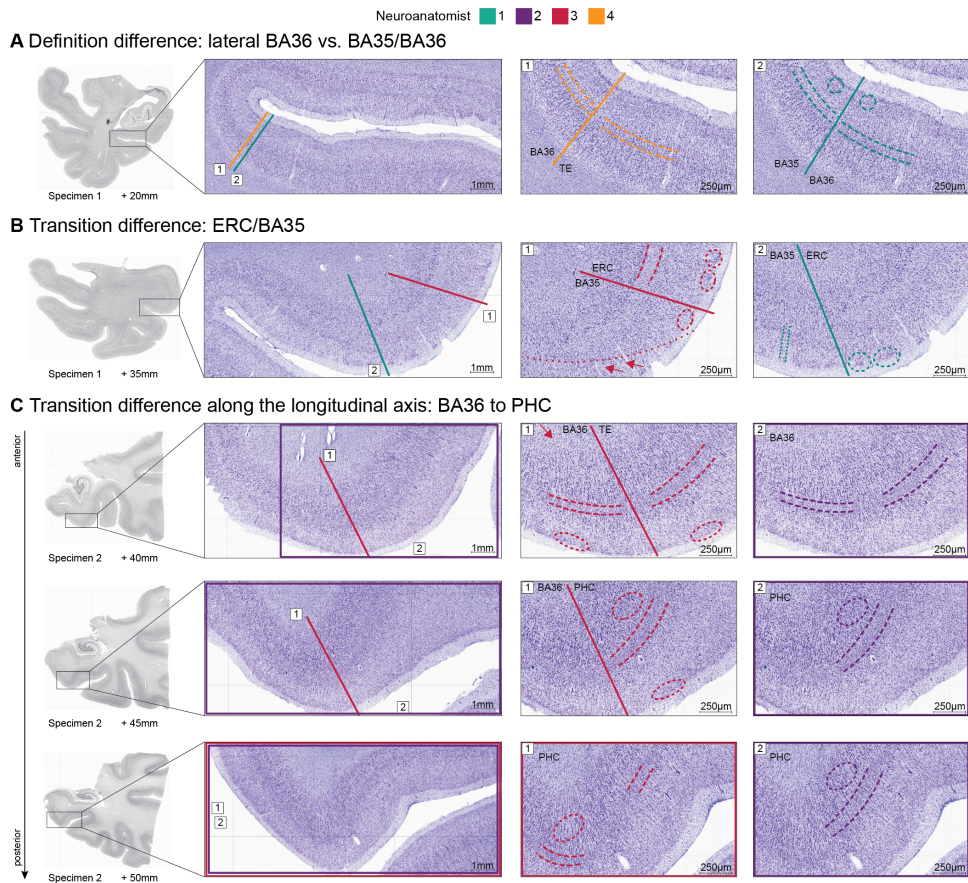

Fig. 9. Differences in delineations in border regions of the MTL cortex due to three reasons.
A: Disagreement in cytoarchitectonic definitions of BA35 and BA36. A1 and A2 highlight the features the neuroanatomists used to inform their annotations. Dashed line: granularity layer, Circle: smaller layer II cells. **B:** Disagreement due to transitional sections. B1 and B2 highlight the features the neuroanatomists used to inform their annotations. Dotted line: wedge-like transition between cortices. Arrows: gradually emerging layer IIIu-cells. Circle: layer II cells. Dashed line: lamina dissecans. Vertical dashed line: columnar organization of cells. **C:** Disagreement due to transition on the longitudinal axis. C1 and C2 highlight the features the neuroanatomists used to inform their annotations. Arrow: transition of grey to white matter. Dashed line: indicates thickness of given cell layer. Circle: density of cells. BA=Brodmann area; ERC=entorhinal cortex; PHC=parahippocampal cortex. Figure reprinted from [308] (CC BY).

These results highlight that definitions and parcellations of the MTL cortex diverge among neuroanatomical schools. That differences exist due to a number of reasons, such as dissimilarities in definitions, increases the understanding of why these differences arise and that some of them may be purely terminological. This sets a crucial foundation to further advance human MTL cortex neuroimaging research and will be used for the development of a harmonized protocol of MTL cortical subregions for in vivo MRI [1], led by the international Hippocampal Subfields Group.

Paper II – part 1

This section described the first part of paper II [310], in which a segmentation protocol for the whole human amygdala on T1-weighted MRI was developed. This was done due to critique of existing segmentations methods, which do not use a multi-atlas approach to perform segmentations that take anatomical variability into account [296, 298, 315, 316, 323].

We found high reliability for the segmentation of the amygdala using the dice similarity index when manually segmenting the amygdala from the same individuals twice (time difference between segmentations=three weeks, DSI=.91±0.02). After implementing the segmentation protocol with the existing T1-ASHS atlas, cross-validation of the automated versus the manual segmentation was performed, which resulted in a DSI=0.88±0.03. In comparison, similar values were found for the anterior hippocampus (DSI=0.91±0.02), posterior hippocampus (DSI=0.89±0.02), and entorhinal cortex (DSI=0.75±0.05). This segmentation pipeline is publicly available (https://www.nitrc.org/frs/shownotes.php?release_id= 7230).

Paper III

Aβ is hypothesized to facilitate the spread of tau pathology beyond the MTL. Yet, there is evidence that, independently of Aβ, age-related tau pathology might be present outside the MTL, which is a topic still under debate. In this study [309], we therefore aimed to investigate age-related tau deposition within and outside the MTL in two independent cohorts. We examined its occurrence independently of Aβ and potential downstream effects on cognition and structural measures in cognitively normal older adults.

This study included 545 cognitively unimpaired individuals (40-92 years) from the BioFINDER-2 study (in vivo) and 639 cognitively unimpaired participants (64-108

years) from the Rush Alzheimer's Disease Center cohorts (ex vivo) [309]. See Table 4.

Table 4. Characteristics of the sample for both cohorts.
Note: mean ± SD and n (%) shown for continuous and categorical variables, respectively. Abbreviations: Aβ=amyloid-beta; CSF=cerebrospinal fluid; mPACC5=modified Preclinical Alzheimer's Cognitive Composite 5; SUVR=standardized uptake value ratio.

	Whole sample	Aβ-negative
BioFINDER-2		
n	545	418
Sex (n, % female)	287 (52.6)	219 (52.3)
Age (years)	65.0 ± 11.7	60.9 ± 11.5
Range	[40-92]	[40-88]
A*POE*-ε4 carrier (%)	48.6	42.3
Education (years)	12.8 ± 3.4	12.9 ± 3.3
mPACC5 (z-scored)	0.06 ± 0.81	0.17 ± 0.76
Episodic memory (z-scored)	-0.23 ± 1.89	0.01 ± 1.81
CSF Aβ42/40 ratio	0.10 ± 0.028	0.11 ± 0.02
Global Aβ-PET SUVR	1.01 ± 0.35	0.85 ± 0.06
ERC/BA35 tau-PET SUVR	1.19 ± 0.49	1.05 ± 0.32
RADC cohorts		
N	639	318
Sex (n, % female)	205 (32.1)	112 (35.2)
Age at death (years)	87.2 ± 7.2	86.0 ± 7.5
Range	[64-108]	[64-108]
Education (years)	16.3 ± 3.7	16.1 ± 3.7
APOE-ε4 **carrier** (%)	93 (16)	35 (11.0)
Aβ load (mean)	1.12 ± 1.04	0.36 ± 0.57
Total tangle density (mean)	3.33 ± 3.78	2.24 ± 2.38
Global cognition (z-scored)	0.14 ± 0.45	0.20 ± 0.44
Episodic memory (z-scored)	0.38 ± 0.57	0.44 ± 0.53

We found that in vivo age-related tau deposition was observed in the MTL but also in frontal and parietal regions, which was independent of Aβ burden (Fig. 10). This finding was also observed when examining only the Aβ-negative individuals. Both findings were validated in the ex vivo cohort (Fig. 10), demonstrating age-related increases in tau aggregates both within and outside the MTL, independent of Aβ. However, more limited regional data was available in the ex vivo cohort, leading to less investigated regions (e.g., some frontal and parietal regions; see Fig. 10).
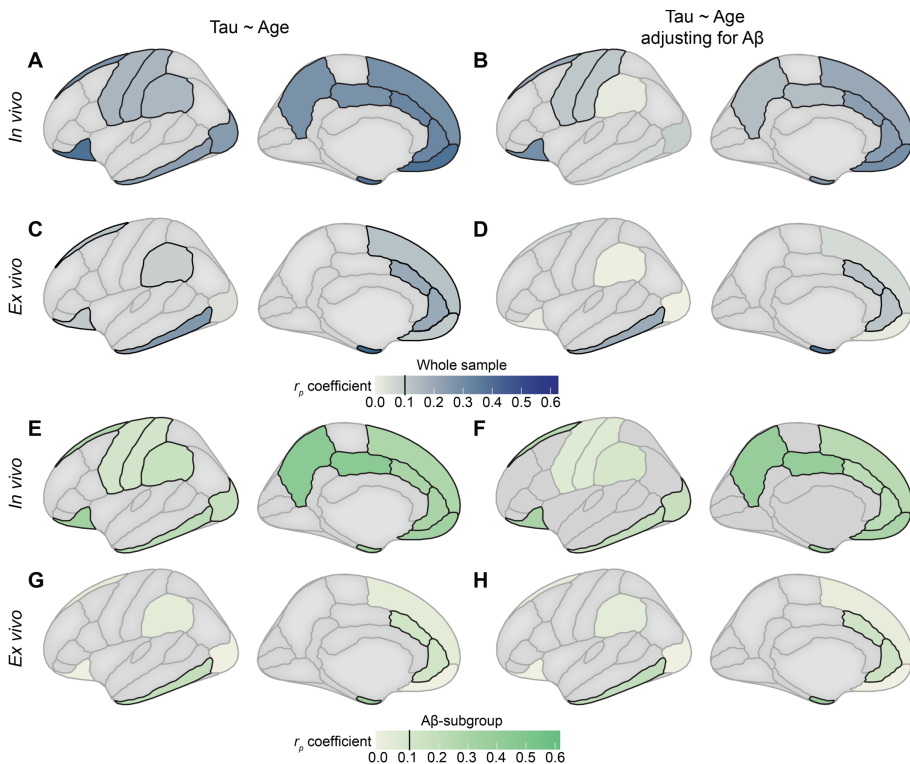
Fig. 10. Associations between age and regional tau-PET uptake.
A: An increase of age is associated with an increase of tau-PET uptake in medial temporal, frontal and parietal regions. **B:** These associations remain significant even when adjusting for regional Aβ-PET. **C-D** show the same associations for the ex vivo cohort. **E-H** additionally show these associations in the Aβ-negative subgroup. Correlations >0.1 are significant at p_{FDR} < 0.05 and outlined dark on the figure. Figure reprinted from [309] (CC BY-NC).

Next, we investigated the association of tau with cortical volume/thickness. The results showed a negative association of regional tau-PET uptake with temporal and parietal regions (Fig. 11A). This was again independent of Aβ. Furthermore, associations between age and cortical volume/thickness were partially mediated by tau in early Alzheimer's disease regions (the subiculum, BA35, precuneus/posterior cingulate, Fig. 11B). The results were similar in the Aβ-negative subgroup where mediations were only observed within the MTL.
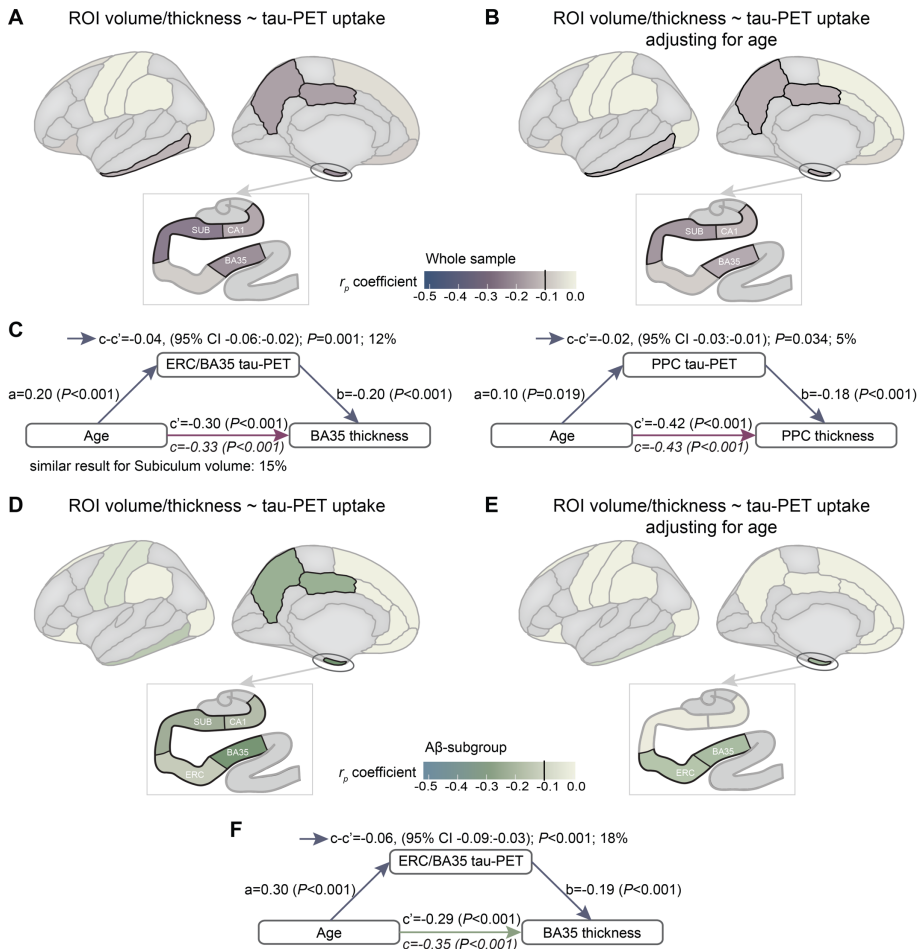
Fig. 11. Associations between age and regional tau-PET uptake with structural measures.
A: An increase of tau-PET uptake was associated with lower thickness/volume in temporal and parietal regions. **B:** The associations of **A** remained statistically significant even when adjusting the models for age. **C:** Partial mediations of regional tau-PET uptake on the association between age and Brodmann area 35 and precuneus/posterior cingulate thickness were observed. **D-F** shows the same associations as A-C in the Aβ- subgroup. Correlations >0.1 are significant at $p_{FDR} < 0.05$ and outlined dark on the figure. Age, sex, and regional Aβ-PET were included as covariates for all associations. Abbreviations: BA=Brodmann area; CA1=Cornu Ammonis 1; ERC=entorhinal cortex; MTL=medial temporal lobe; PPC=precuneus/posterior cingulate cortex; ROI=region of interest; SUB=subiculum. Figure reprinted from [309] (CC BY-NC).

Finally, we observed that the association between age and cognitive performance was partially mediated by MTL tau-PET uptake, even when including Aβ as covariate, which was supported by similar findings in the ex vivo cohort (Fig. 12).
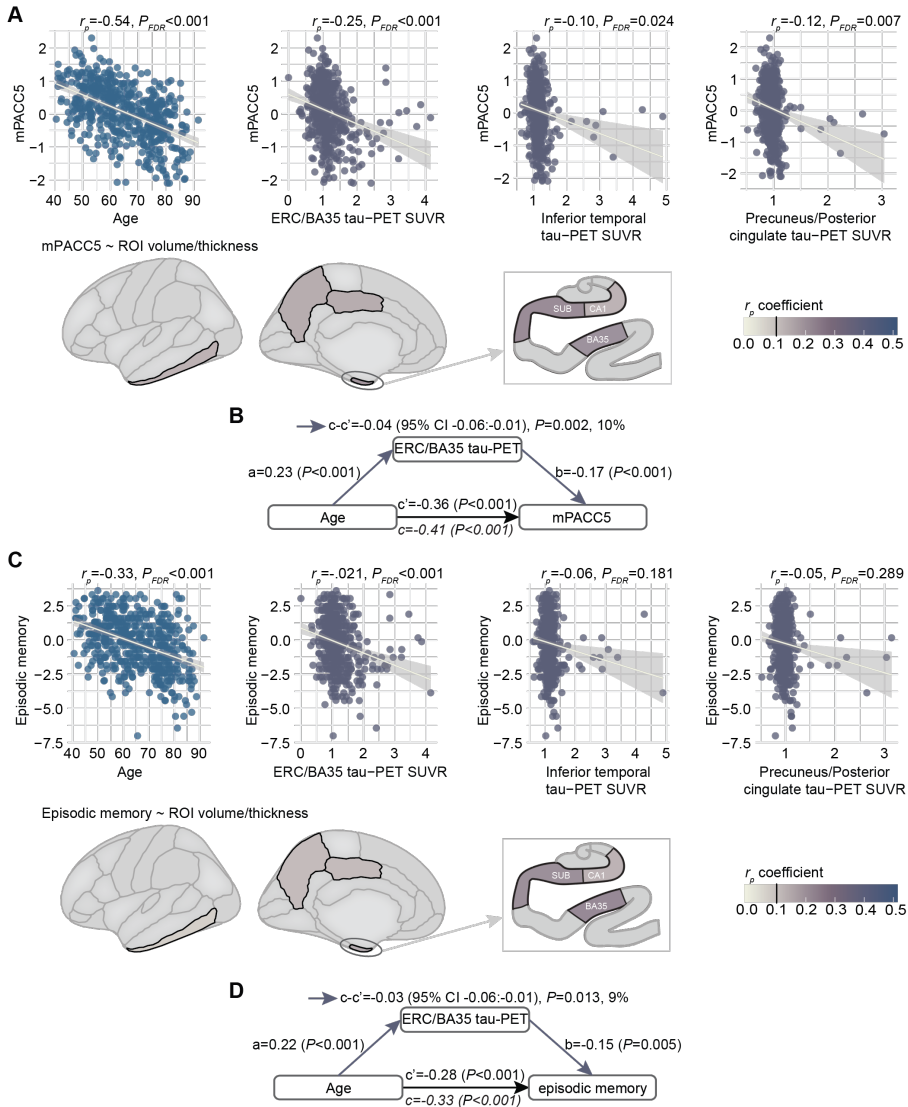
Fig. 12. Associations between age, tau-PET uptake, and regional volume/thickness with cognitive performance in the whole in vivo cohort.
A: Associations between tau-PET uptake, age and regional volume/thickness with global cognition. **B:** Partial mediation of MTL tau-PET on the association between age and global cognition. **C:** Associations between tau-PET uptake, age and regional volume/thickness with episodic memory performance. **D:** Partial mediation of MTL tau-PET on the association between age and episodic memory performance. Correlations >0.1 are significant at p_{FDR} < 0.05 and outlined dark on the figure. Age, sex, and regional Aβ-PET were included as covariates for all associations. Abbreviations: BA=Brodmann area; CA1=Cornu Ammonis 1; ERC=entorhinal cortex; mPACC5=modified Preclinical Alzheimer's Cognitive Composite; SUB=subiculum; SUVR=standardized uptake value ratio. Figure reprinted from [309] (CC BY-NC).

Taken together, this study provides in vivo and ex vivo evidence supporting the presence of tau pathology in aging and potential PART outside the MTL. The autoradiography results, not shown here, further support that tau pathology in PART cases can potentially be detected using the [^{18}F]-RO948 PET-tracer. Our results demonstrate that age-related, Aβ-independent tau pathology can impact downstream effects on brain structure and cognition. This has implications for our understanding of tau spreading and accumulation outside the medial temporal lobe, also in the context of Alzheimer's disease. Moreover, this study suggests the potential utility of tau-targeting therapies in individuals with no or low Aβ pathology.

Paper IV

Tau pathology has been shown to be closely linked to cognitive decline in Alzheimer's disease. Neurodegeneration is one of the putative mechanisms through which tau may exert negative effects on cognitive functioning. However, prior work has focused on these association using coarse neurodegeneration measures and utilized cognitive composite measures that may not be sensitive to differences in certain cognitive subdomains. Thus, the aim of this study was to investigate potential mediating effects of MTL and neocortical structural measures for cognitive subdomains in typical Alzheimer's disease.

To this end, we investigated 319 individuals that are Aβ+ and are cognitively unimpaired, MCI or Alzheimer's disease participants of the ADNI cohort (age: 72.8±6.86 years, 51.4% female, Table 5). As discussed in the methods, cognitive subdomain measures have been adjusted for other cognitive measures in order to obtain purer measures of the given function.

Table 5. Characteristics of the sample.
Note: mean ± SD and n (%) shown for continuous and categorical variables, respectively. Abbreviations: AD=Alzheimer's disease; APOE=apolipoprotein E; CU=cognitively unimpaired; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination.

	Overall	**CU**	**MCI**	**AD**
N	319	149	134	36
Age	72.8 ± 6.86	72.7 ± 6.25	72.4 ± 7.07	74.9 ± 8.17
Sex (female) n (%)	164 (51.4)	93 (62.4)	58 (43.3)	13 (36.1)
Education (years)	51.0 – 69.0	70.3 – 85.0	50.9 – 69.4	70.1 – 85.1
***APOE*-ε4 +** n (%)	171 (53.6)	70 (46.9)	75 (55.9)	26 (72.2)
MMSE total score	27.2 ± 3.13	28.8 ± 1.34	26.5 ± 3.47	23.4 ± 2.79

Prior to investigating mediation models, we first examined the associations between tau-PET uptake, structural measures, and the cognitive subdomains. This was a

necessary step prior to fitting mediation models. The results showed that higher tau-PET uptake in both MTL and neocortical composite regions were associated with lower performance on all cognitive subdomains. Statistically significant associations indicated additionally that higher tau-PET uptake was associated with lower structural thickness/volume, except for the frontal regions. Finally, positive associations were found between the structural thickness/volumes and better performance on the cognitive subdomains. However, not all regional measures were significantly associated with all cognitive subdomains (see the paper in the appendix for more information).

In the next step we fit separate mediation models for only the regional measures that were both associated to the tau-PET composites and the cognitive subdomains. The results showed that MTL and neocortical measures were mediating the associations between tau-immediate recall and tau-delayed recall (Fig. 13). Only MTL subregional thickness/volume were mediators for the tau-late recall, tau-recognition, and tau-executive function associations, while only neocortical regional thicknesses were mediating the tau-semantic fluency associations.
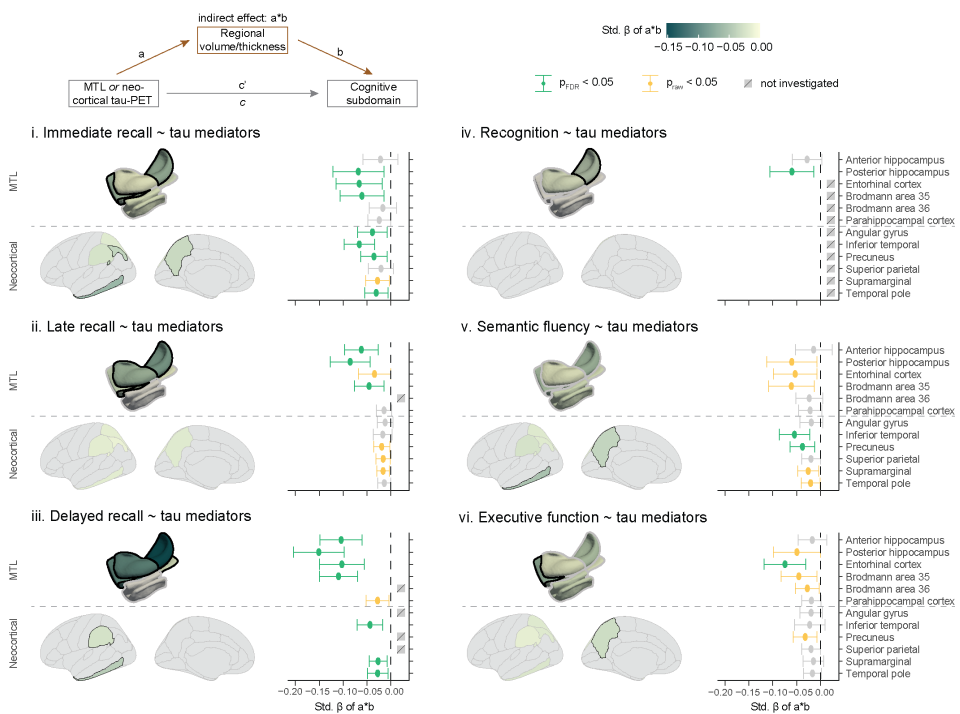

Fig. 13. Structural mediators for the associations between tau and cognitive subdomains.
A black outline indicates a significant mediating effect (p_FDR<0.05). Abbreviations: BA=Brodmann area; MTL=medial temporal lobe; PET=positron emission tomography; std. β of a*b=standardized β coefficient of the mediating effect.

In a next step, we aimed to fit complex mediation models. The purpose of this analysis was to understand if certain regions are uniquely mediating a given tau-cognition association. Prior to fitting these models, we investigated if MTL and neocortical tau-PET composites remained significantly associated to the cognitive domains when included in one regression model (see Fig. 14A). The results indicated that MTL tau-PET uptake was negatively associated to the memory domains, while neocortical tau-PET uptake was negatively associated to executive function. Both tau-PET composites were negatively associated with semantic fluency. Only the significant tau-PET composites were used to fit the complex mediations for a given cognitive subdomain.

The complex mediations indicated that different MTL subregions are mediating episodic memory subdomains (hippocampus and extra-hippocampal MTL regions for tau-immediate recall and -delayed recall associations; only hippocampus for tau-late recall and tau-recognition associations, Fig. 14A). Additionally, the inferior temporal gyrus was observed to be a relevant region mediating the tau-semantic fluency association, albeit only at trend level. No mediator was found for the tau-executive function association.
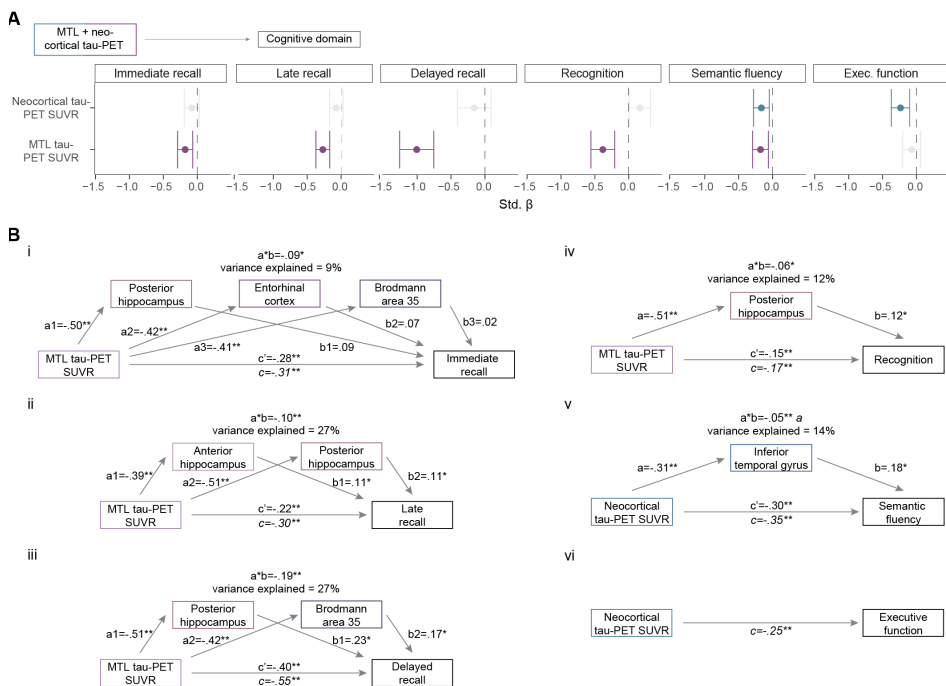
Fig. 14. Complex mediation analyses for the associations between tau and cognitive subdomains. A: Associations of tau-PET composites with the cognitive subdomains when included in one regression model B: Results of the complex mediation models per cognitive subdomain. Abbreviations: a*b=standardized β coefficient of the mediating effect; BA=Brodmann area; MTL=medial temporal lobe; PET=positron emission tomography; std. β of a*b=standardized β coefficient of the mediating effect.

To summarize, associations of tau-PET uptake with the memory subdomains and semantic fluency, but not for executive function, were partially mediated by structural MRI measures in a region-specific manner. The results of this study suggest that macrostructural changes play a role in the pathway between tau and cognitive subdomains. However, given the relatively low variance explained by these mediation models, other mechanistic pathways, such as microstructure and synaptic dysfunction, should be investigated further [43, 263]. Given our results, Brodmann area 35 and inferior temporal gyrus are relevant regions that should be explored further in this context. In a similar line of reasoning, also the adjustments for the cognitive subdomains to obtain purer measures require further validation. Our results suggest that we obtain reasonable biological substrates of cognitive subdomains using these adjustments, indicating its utility for other cognitive measures. This could aid in using more sensitive cognitive measures in the future.

Paper II – part 2

The clinical part of *paper II* focused on the MTL atrophy patterns in individuals with a clinical onset of Alzheimer's disease before the age of 65 years, commonly classified as early-onset Alzheimer's disease [193]. The MTL has been found to be relatively spared in early-onset Alzheimer's disease [50, 108, 195] compared to late-onset Alzheimer's disease. Yet, prior research often defined early-onset Alzheimer's disease purely by age of onset, grouping various clinical phenotypes together and lacking biomarker confirmation of Alzheimer's disease. We aimed to compare atrophy in amnestic early- versus late-onset cognitive impairment, also with respective control groups (young vs. older), and associations with co-pathologies. For information about the final sample, see Table 6 [310].

Table 6. Characteristics of the sample.
Note: mean ± SD and n (%) shown for continuous and categorical variables, respectively. Abbreviations: Aβ=amyloid-beta; AD=Alzheimer's disease; aEOAD=amnestic early-onset cognitive impairment, aLOAD=amnestic late-onset cognitive impairment; *APOE*=apolipoprotein E; CU=cognitively unimpaired; CSF=cerebrospinal fluid; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; OCU=older cognitively unimpaired controls; SD=standard deviation; YCU=younger cognitively unimpaired controls.

	YCU	OCU	aEOAD	aLOAD	Total
N	188	151	41	154	534
Diagnosis CU/MCI/AD	188 (100) / 0 (0) / 0 (0)	151 (100) / 0 (0) / 0 (0)	0 (0) / 16 (39.0) / 25 (61.0)	0 (0) / 65 (42.2) / 89 (57.8)	339 (63.5) / 81 (15.2) / 114 (21.2)
Sex (f)	103 (54.8)	99 (65.5)	20 (48.8)	82 (53.2)	304 (56.9)
Age (years)	58.6 ± 4.89	77.3 ± 3.38	61.0 ± 4.82	76.2 ± 3.92	69.2 ± 9.76
Range	51.0 – 69.0	70.3 – 85.0	50.9 – 69.4	70.1 – 85.1	50.9 – 85.1
Education (years)	13.2 ± 3.12	12.4 ± 3.74	14.1 ± 3.33	12.5 ± 4.79	12.8 ± 3.86
APOE-ε4 +	85 (45.2)	29 (19.2)	25 (61.0)	114 (74.0)	253 (47.4)

| CSF Aβ42/40 + | 0 (0.0) | 0 (0.0) | 41 (100) | 154 (100) | 195 (36.5) |
| MMSE score | 29.2 ± 0.92 | 28.8 ± 1.20 | 24.6 ± 3.22 | 24.4 ± 2.53 | 27.3 ± 2.87 |

MTL atrophy patterns were similar for both the amnestic early- and late-onset groups, showing smaller MTL subregional thickness/volume in all MTL subregions compared to controls (Fig. 15). Nevertheless, amnestic late-onset Alzheimer's disease showed thinner entorhinal and parahippocampal cortices and lower hippocampal subfield volumes than the amnestic early-onset group (Fig. 15). In line with previous reports, amnestic early-onset Alzheimer's disease had relative thinner cortex in parietal regions than the amnestic late-onset group (Fig. 16).
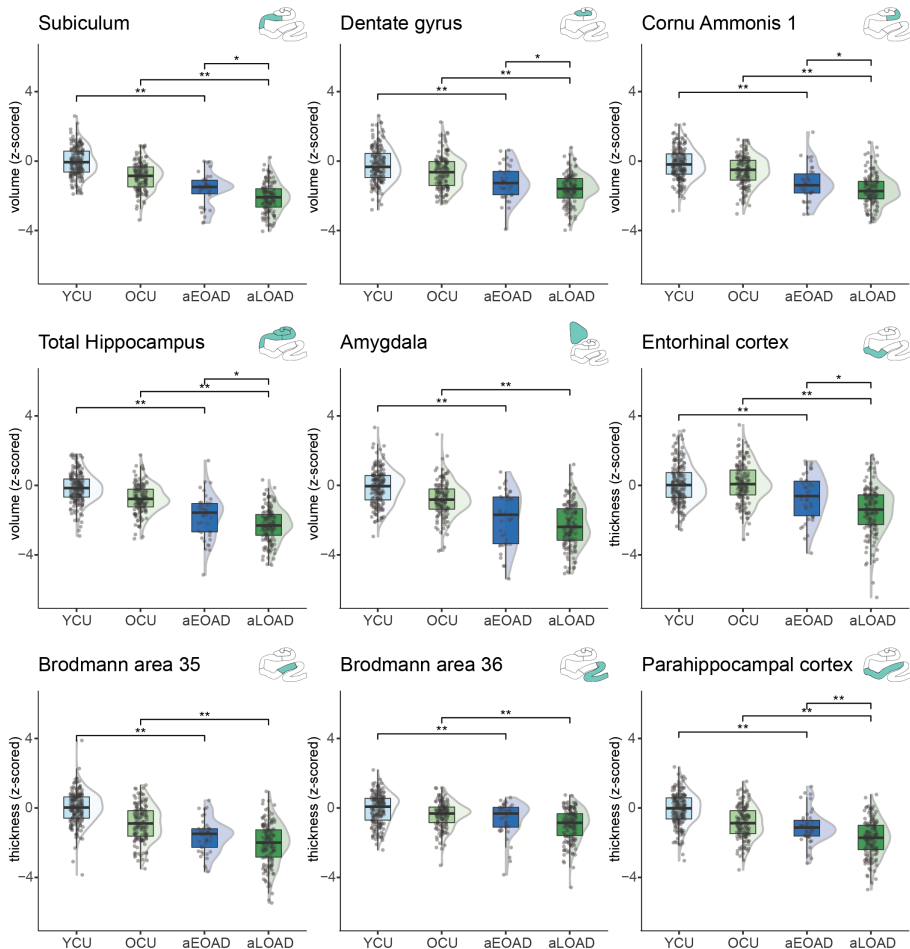

Fig. 15. Results of the comparisons between MTL subregions for aEO- and aLOAD groups with each other and respective controls.

*=p_{FDR}<.05; **=p_{FDR}<.001. Abbreviations: aEOAD=amnestic early-onset Alzheimer's disease; aLOAD=amnestic late-onset Alzheimer's disease; OCU=older cognitively unimpaired controls; YCU=younger cognitively unimpaired controls. Figure reprinted from [310] (CC BY).
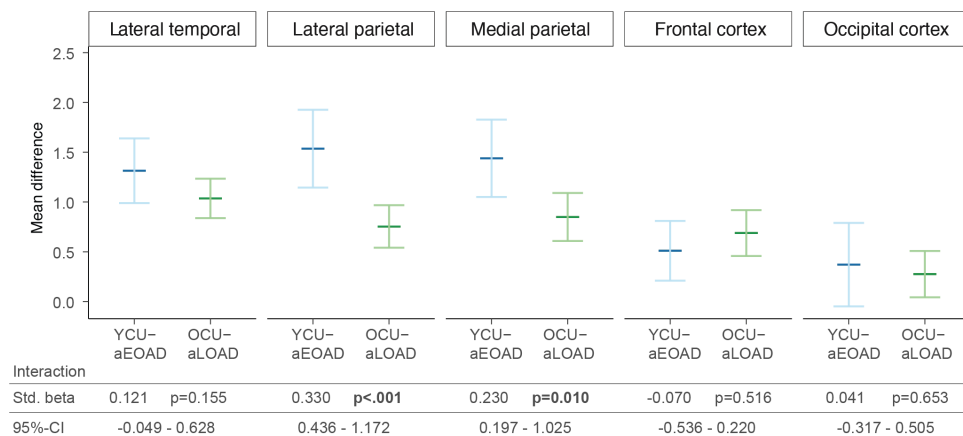

Fig. 16. Mean differences of the Alzheimer's disease groups with respective controls indicate significant differences for parietal regions.
Abbreviations: aEOAD=amnestic early-onset Alzheimer's Disease; aLOAD=amnestic late-onset Alzheimer's disease; OCU=older cognitively unimpaired controls; YCU=younger cognitively unimpaired controls. Figure reprinted from supplementary information of [310] (CC BY).

When exploring Alzheimer's disease and co-pathologies, we found that the amnestic early-onset group showed lower white matter hyperintensities than amnestic late-onset Alzheimer's disease (Fig. 17). However, no differences in MTL tau-PET or our proxy of TDP-43 positivity, based on the ratio of anterior hippocampus and parahippocampal cortex [93], were found.
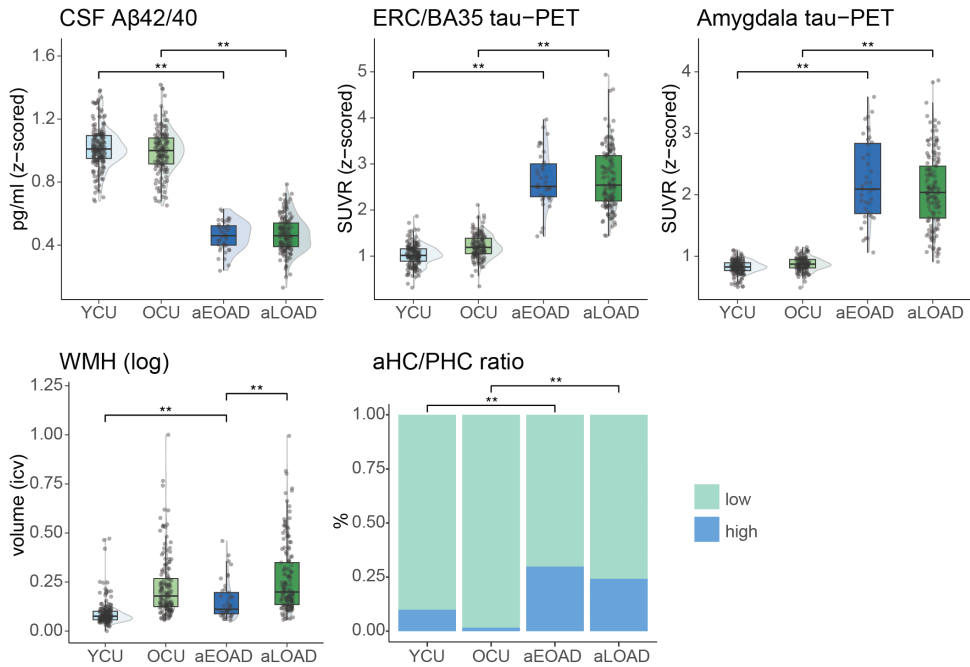
Fig. 17. Group comparisons of aEO- and aLOAD groups with each other and respective controls for Alzheimer's disease-related biomarkers and co-pathologies.
*=p_{FDR}<.05; **=p_{FDR}<.001. Abbreviations: Aβ=amyloid-beta; aHC/PHC ratio=ratio of anterior hippocampus and parahippocampal cortex; aEOAD=amnestic early-onset Alzheimer's disease; aLOAD=amnestic late-onset Alzheimer's disease; CSF=cerebrospinal fluid; PET=positron emission tomography; SUVR=standardized uptake value ratio; OCU=older cognitively unimpaired controls; WMH=white matter hyperintensities; YCU=younger cognitively unimpaired controls. Figure reprinted from [310] (CC BY).

To summarize, the results show evidence for MTL atrophy in amnestic early-onset Alzheimer's disease in a similar manner as the amnestic late-onset Alzheimer's disease group, albeit differences were observed. Additionally, overall similar levels of MTL tau pathology and co-pathologies were observed in comparison to amnestic late-onset Alzheimer's disease and only a difference in white matter hyperintensities was found between amnestic early-onset and late-onset Alzheimer's disease. This suggests that mechanisms driving amnestic symptoms and MTL atrophy patterns in both amnestic early- and late-onset Alzheimer's disease may be largely similar.

Paper V

Historically, investigations of neurodegeneration with MRI primarily focused on atrophy in the hippocampus. This focus was based on the hypothesis that this

atrophy is indicative of the presence of tau pathology. Yet, cumulating evidence suggests that different neuropathologies are present in the MTL and can lead to or contribute to neurodegeneration in the MTL [98, 123, 166, 207, 208, 240]. While previous work has shown that NFT pathology occurs in certain regions earlier than others (Fig. 18A), the same is true for TDP-43 (Fig. 18B), potentially additionally contributing to MTL neurodegeneration. The regions affected earliest by these pathologies are not the same (transentorhinal cortex versus amygdala, respectively). Yet, there is a large spatial overlap of where these pathologies accumulate in the MTL. This shows the relevance of understanding possible synergistic or additive effects of these pathologies, which is supported by the observation that NFT and TDP-43 pathology co-occur (Fig. 18C). It is unclear what the relative contribution of NFTs and TDP-43 pathology on MTL atrophy is. Thus, in this paper [302], we aimed to (i) increase the understanding of the contribution of NFTs and TDP-43 to MTL atrophy, (ii) put forward hypotheses about these associations, and (iii) formulate future directions of research in this context.
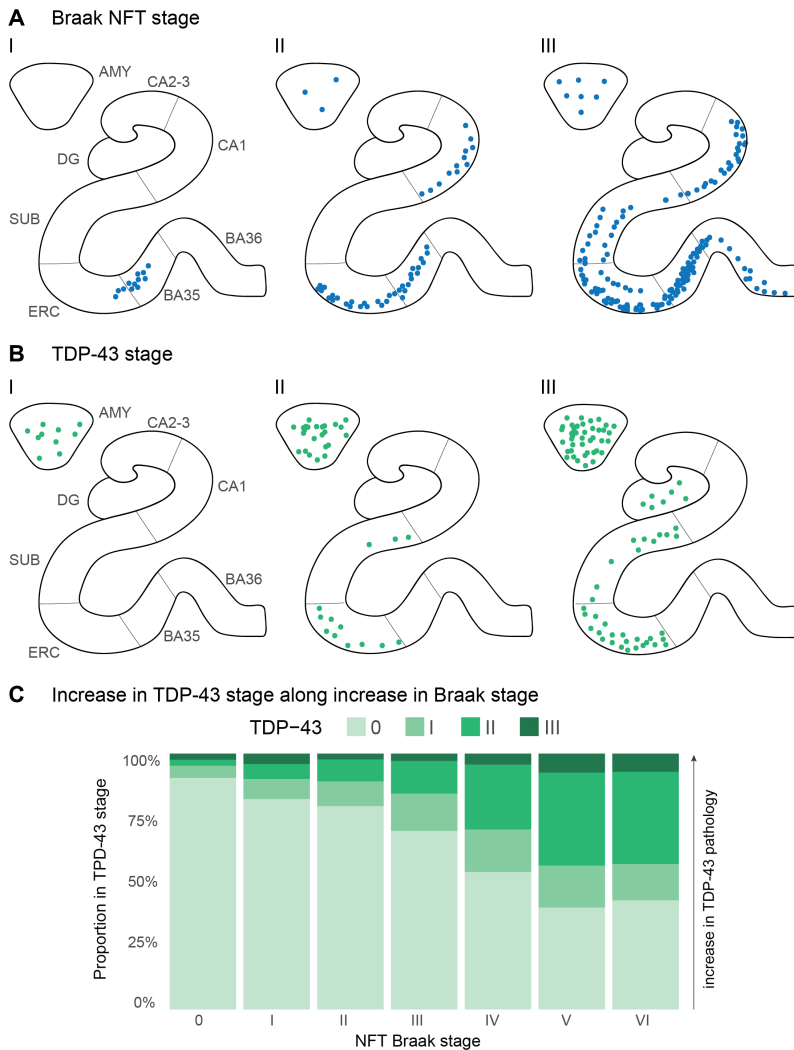
Fig. 18. Staging of NFT and TDP-43 pathologies and their association.
A: An overview showing the Braak staging of tau NFT pathology, limited to the MTL regions invovled [35]. **B:** An overview of the staging of TDP-43 pathology, again limited to the MTL regions [207, 208]. **C:** An overview of the association between increasing stages of NFTs and TDP-43. The data was extracted from Nelson et al., 2022 [206]. Abbreviations: ERC=entorhinal cortex; LATE-NC=Limbic-predominant Age-related TDP-43 encephalopathy; NFT=neurofibrillary tangles; TDP-43=TAR DNA-binding protein 43 kDa. Figure reprinted from [302] (CC BY-NC-ND).

The literature review indicated that both NFT and TDP-43 pathology are associated with MTL atrophy, even when controlling for each other as well as other pathologies. This evidence primarily stems from postmortem studies and research linking antemortem MRI with postmortem neuropathological measures, allowing

the measure of fine-grained MTL subregions. Due to the absence of in vivo biomarkers of TDP-43, the investigation of TDP-43 effects on in vivo MTL atrophy is more limited, leading to poorly understood longitudinal effects of TDP-43. However, postmortem studies support the negative effects of TDP-43 pathology on structural MTL changes. Few studies did not observe associations between the pathologies with MTL atrophy. These studies seemed to be limited by small sample size and thereby power and by the semi-quantitative scores common in neuropathological investigations.
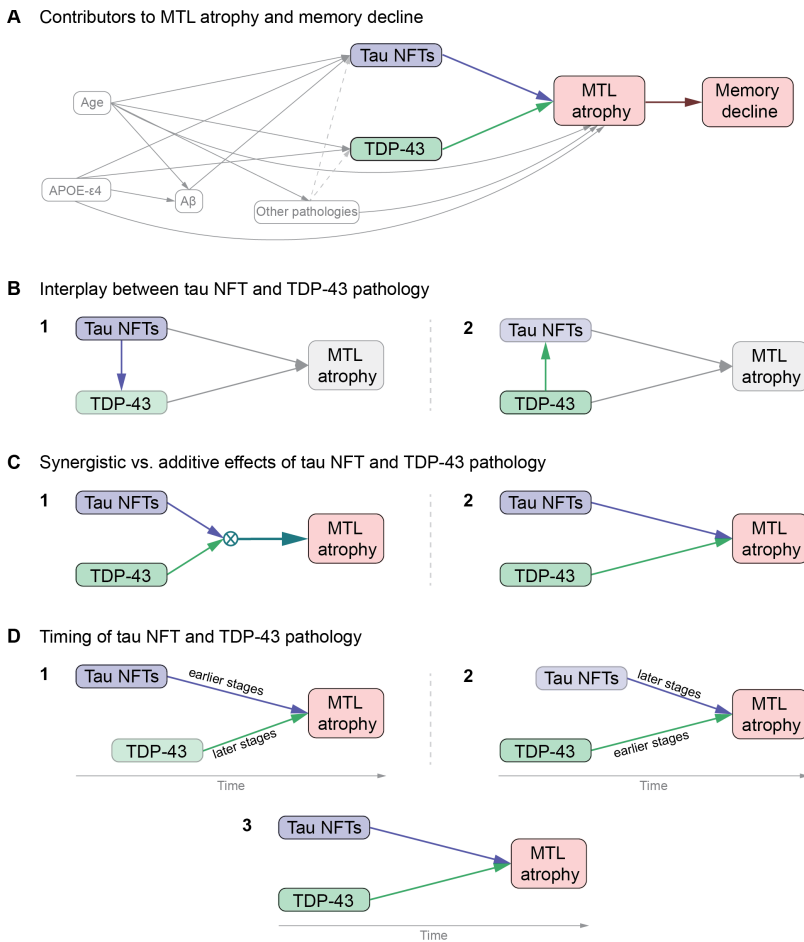
Fig. 19. Hypotheses about the interplay, synergism, and timing between tau NFT and TDP-43 pathologies.
A: Overview of different contributing factors to MTL atrophy and memory decline. **B:** Potential interplay between tau NFTs and TDP-43 may be due to potentiating effects of one pathology on the other. **C:** Potential synergistic (1) or additive (2) effects of tau NFT and TDP-43 pathology. **D:** Different timing of tau NFT and TDP-43 pathology are conceivable, with one pathology occuring first (1, 2) or similar time of occurrence (3). Abbreviations: Aβ=β-amyloid; CVD=cerebrovascular disease; NFT=neurofibrillary tangles; TDP-43=TAR DNA-binding protein 43 kDa. Figure reprinted from [302] (CC BY-NC-ND).

Based on the review of the literature, we provide an overview of potential alternative hypotheses regarding interplay, synergism and timing of tau NFTs and TDP-43 pathology (Fig. 19), which have yet to be determined. The first hypothesis focused on interplay, since it is possible that either tau NFTs or TDP-43 pathology potentiate each other leading to more accumulation of one of the pathologies (Fig. 19B). Second, it remains to be determined whether the effects on MTL atrophy of the pathologies are synergistic or additive (Fig. 19C). Finally, while there is some evidence for an earlier occurrence of tau NFTs compared to TDP-43 pathology, further investigation is required in understanding the timing of the detrimental effects of the pathologies on MTL structure (Fig. 19C).

A better understanding of how co-occurring pathologies, such as tau NFTs and TDP-43, contribute to atrophy in the MTL is needed. One main contributor to this is a valid and reliable in vivo biomarker of TDP-43 pathology, allowing the investigation of potential interactions over time. Additionally, increasing knowledge concerning the interplay between tau NFTs and TDP-43 could be achieved by, for example, investigating more granular measures or increasing the number of cohorts including antemortem and postmortem imaging [302]. This is of importance for enrollment and design of clinical trials, such as understanding the timing of potential future interventions, and allows for controlling the participants that have (concomitant) LATE-NC.

Discussion and future perspectives

Given the relevance of the MTL, specifically its subregions, in the context of aging and Alzheimer's disease, the work presented in this thesis had two overarching objectives to: (i) contribute to the methodological advancements of MRI-based measures of MTL subregions and (ii) characterize MTL subregional atrophy and its contributions to cognitive decline in aging and Alzheimer's disease. We used a translational approach, ranging from postmortem histology to in vivo neuroimaging to reach these objectives.

To summarize the contributions to the first objective, we observed that definitions and parcellations of the MTL cortex differ among neuroanatomical laboratories and described why these differences arise (*paper I*; [308]). We additionally developed a reliable segmentation protocol of the whole amygdala for T1-weighted MRI (*paper II – part 1*; [310]), further contributing to methodological advancements of measuring MTL subregions reliably.

To contribute to the second objective, we focused on specific settings where the granular understanding of these regions is hypothesized to provide additional value. First, we found that Aβ-independent age-related tau-PET uptake within the MTL was linked to downstream effects on Brodmann area 35 thickness as well as episodic memory in cognitively unimpaired older adults (*paper III*; [309]), highlighting the relevance of measuring granular MTL subregions in this context. Second, we found that specific MTL subregions partially mediated the associations between tau and specific cognitive subdomains in individuals on the typical Alzheimer's disease continuum (*paper IV*). This contributed to a nuanced understanding of which regional neurodegeneration is involved in tau-induced changes in different cognitive processes, highlighting that subregional differences exist, and that studying these provides valuable information. Third, largely similar patterns of MTL atrophy between amnestic early-onset and late-onset Alzheimer's were observed (*paper II – part 2*; [310]), highlighting that fine-grained measures (and differentiation between phenotypes) are important to investigate as they add information that coarse measures cannot capture. Finally, both NFT and TDP-43 pathologies contribute to neurodegeneration in the MTL and may affect different subregions at different stages (*paper V*; [302]), underscoring the importance of further granular investigations. Overall, investigating MTL subfields in aging, individuals on the typical Alzheimer's disease continuum, and amnestic early-onset Alzheimer's

disease allows a more detailed characterization of neurodegenerative processes in these regions.

In the following sections, overarching themes of these studies and their implications will be discussed for the two main objectives. Detailed discussions of the individual projects can be found in the discussion sections of the respective studies in the appendix.

Advancements in measuring MTL subregions in vivo

Since the first neuroimaging studies in Alzheimer's disease, many advances to measure the granular regions of the MTL on in vivo MRI have been made. The field started to investigate subregions of the MTL, driven by the understanding that specific regions (e.g., transentorhinal cortex) are selectively vulnerable to early pathology [37, 177]. While neuroanatomy has historically guided MRI segmentation, the increasing use of MRI has highlighted the substantial inter-individual anatomical variability which complicates reliable parcellation. This heterogeneity is recognized by neuroanatomists, which is documented, for example, for different MTL sulcal patterns [69, 129]. Yet, standard neuroanatomical atlases do not readily capture this variability, since they are often based on detailed analysis of single specimen. This is due to the substantial amounts of time and effort required to label one specimen [e.g., 68, 182]. Due to this single-case approach, translating the neuroanatomical information to neuroimaging research has been challenging as it is not representative of the anatomical variability known to exist.

Further complicating the translation of neuroanatomical knowledge to neuroimaging is the existence of different neuroanatomical schools. These schools have historically evolved from distinct foundational work [308]. For example, Von Economo & Koskinas [82] and Brodman [42] published different cortical maps, resulting in varying terminology and definitions used for brain parcellation. This divergence may not be immediately obvious to researchers seeking to apply neuroanatomical insights to neuroimaging studies. The direct comparison and integration of information across these different neuroanatomical schools pose an additional challenge to the effective interpretation of this knowledge. Finally, the differences between studied specimen but also between neuroanatomy schools has led to different parcellation schemes in in vivo neuroimaging [318], which can hinder the comparison of study results.

Our study (***paper I***) offers a significant contribution to these challenges by both elucidating the difficulties in translating neuroanatomical knowledge and providing a comparative overview of differing definitions and parcellations across neuroanatomical schools. By having multiple expert neuroanatomists perform parcellations on the same specimen, we enabled a direct comparison of these

variations. Systematically summarizing the subregion definitions and resulting parcellations, we identified underlying reasons observed for discrepancies. Importantly, this variability is not indicative of methodological errors or oversight by the highly experienced neuroanatomists, supported by overlap of various parcellations, but rather reflects the inherent complexity of defining some of these structures. This complexity stems from several factors: first, the gradual, rather than sharp, boundaries between subregions and the compression of cortical layers within sulcal fundi and gyri complicate precise delineation. Second, the reliance on different types of anatomical information, including macrostructural features, may contribute to discrepancies. Therefore, ongoing collaboration among neuroanatomical laboratories to address these discrepancies will be crucial for harmonizing definitions in the future. While harmonization of the neuroanatomical field would be beneficial, it is still far from being achieved. In the meantime, it is crucial to be aware of these inherent variabilities when interpreting neuroimaging data.

As above-mentioned, a multitude of different in vivo MRI segmentation protocols is currently in use [318], which is based on the differences in neuroanatomical schools and difficulties parcellating the MTL. Thus, harmonization of segmentation protocols for the MTL would facilitate direct comparisons between studies, making this an important step for MTL neuroimaging research. One such harmonization effort is led by the Hippocampal Subfields Group (https://hippocampalsubfields.com/) [211, 299]. This is an international group of researchers who are aiming to establish a harmonized MTL segmentation protocol for in vivo MRI. A subgroup of the Hippocampal Subfields Group, the MTL cortex working group, is utilizing the information presented in *paper I* to establish a harmonized segmentation protocol for the extra-hippocampal MTL cortex [1], a group I am actively involved in. This protocol will be integrated with those developed by other working groups within the Hippocampal Subfields Group focusing on different hippocampal regions, ultimately leading to a comprehensive, harmonized segmentation protocol for the entire MTL. The establishment of a widely adopted harmonized protocol will not only enhance our understanding of age-related and dementia-related changes in the MTL but also accelerate the process of these insights across research groups. Improving the consistency and accuracy of cortical MTL subregional segmentations is paramount for advancing MTL neuroimaging research, not only in the context of aging and Alzheimer's disease but all research focusing on the MTL (e.g., epilepsy).

This thesis additionally contributed to methodological advancement in measuring MTL subregions by developing a segmentation protocol for the whole amygdala for T1-weighted MRI (*paper II – part 1*). This region is known to exhibit early pathological changes but has been less extensively studied in Alzheimer's and related disease research [269]. Our protocol provides reliable demarcation of the amygdala and has been integrated into the existing ASHS segmentation pipeline,

enhancing its ease of use. Since ASHS utilizes a multi-atlas approach, anatomical variability is considered. This updated ASHS package is currently utilized by our research group in Lund and the group developing ASHS at UPenn. Moreover, the protocol has been adopted by several external sites, including the German Center for Neurodegenerative Diseases, Germany [17] and the University of San Francisco, USA [97], highlighting the interest in investigating the amygdala as well as the practical utility of our protocol.

While contributions to advancing subregional MTL measures have been made here, it is crucial to consider the broader implications of this work beyond the MTL. The challenge of individual heterogeneity is not limited to the MTL. Other regions show large inter-individual variability as well [e.g., 288] and the fundamental differences in the foundational work by Von Economo & Koskinas [82] and Brodman [42], which delineated whole brains, also apply to other brain regions. The presented findings (*paper I*) underscore that the underlying "ground truth" of neuroanatomy is more complex than potentially assumed. Consequently, it is essential to be mindful of the potential impact of this inter-individual variability on currently employed segmentation tools for neocortical areas. Furthermore, the harmonization efforts currently underway for the MTL may serve as a valuable model for similar initiatives in other brain regions. The Thalamic Nuclei Neuroimaging Group (https://thalamicsegmentation.github. io/index.html) is one such example, aiming to establish an in vivo MRI segmentation protocol for thalamic nuclei.

To summarize, several contributions to the methodological advancements for MTL subregions measurements have been made, which additionally have broader implications for neuroimaging studies in terms of ensuring anatomically correct segmentations.

The importance of characterizing MTL atrophy

Consistent with the rationale underpinning this thesis, the reliance of more macroscopic measures of the MTL, such as total hippocampal volume, obscures the depth of information obtainable from this region. This is particularly important concerning early and nuanced subregional variation that may provide valuable insights into different disease mechanisms and may hold prognostic significance. The importance of investigating MTL subregions in aging and Alzheimer's disease is supported by the findings presented throughout this thesis. First, *paper III* highlighted that specific MTL subregions are affected earliest in aging and possible PART. Second, *paper IV* provided an increased granular understanding that early tau-induced cognitive decline partly depends on neurodegeneration in specific MTL subregions. Third, *paper II – part 2* showcased the utility of investigating fine-grained MTL subregions to characterize amnestic early-onset Alzheimer's disease.

Overall, these examples support that granular information of the MTL in different contexts is important to pinpoint earliest changes and neurobiological substrates of cognitive decline.

The keywords of *fine-grained*/*granular* and *subtle* stand out when discussing the work of this thesis and connect to several important considerations for future research. First, while we contributed to a nuanced understanding of which regions are involved in tau-induced changes in different cognitive processes (***paper IV***), it also became apparent that even more granular investigations may be of importance. Given that the MTL subregional thickness/volume measures did not explain the associations between tau-PET uptake and cognitive subdomains fully, microstructural changes, synaptic dysfunction, and/or neuroinflammation likely contribute to cognitive impairment, factors that are not readily captured by structural MRI. For example, recent advances in diffusion MRI (dMRI) sequences and modeling allow the investigation of grey matter microstructure [43, 263, 264]. Investigating microstructural changes within specific regions highlighted by this work (e.g., Brodmann area 35) may be even more uniquely suited to detect subtle early changes and should, thus, be investigated further [43, 263, 264]. Second, fine-grained investigations are not only important for MTL subregions, but this reasoning can also be applied to measurements of cognitive function. The unique approach utilized here for the isolation of functions of cognitive subdomains (***paper IV***) provided plausible biological substrates. This indicates its utility and warrants further research, which can be readily implemented using standard cognitive testing. Additionally, improvement in measures of cognitive functions, specifically for cognitive subdomains, is of relevance to monitor subtle changes in cognitive performance. While endeavors to develop more sensitive cognitive measures, such as digital cognitive assessment, are ongoing [225], fine-grained cognitive measures should be prioritized in Alzheimer's disease research, especially in preclinical or asymptomatic stages. This is because these fine-grained measures are likely able to assess *subtle* changes or deficits in cognition. Thus, these measures may be able to highlight cognitive deficits that are currently not captured by standard methods. This is, however, relevant for preclinical trials. Additionally, specific cognitive deficits may directly impact patient's daily lives, ultimately leading to more clinically relevant and patient-centered research outcomes. Third, the reasoning that fine-grained investigations are of importance is also applicable to the heterogeneous presentations of aging and Alzheimer's disease in general. As such, the grouping of phenotypes or different groups may dilute group differences and hampers our understanding of dissimilarities, as shown for amnestic early-onset Alzheimer's disease in ***paper II – part 2***. Overall, these considerations are important for future investigations and will allow detailed characterization of cognitive decline in aging and Alzheimer's disease.

In order to capture such fine-grained and potentially subtle changes in future research, specifically in early stages or in specific phenotypes, also a *longitudinal*

characterization of *papers II-IV* is required in order to understand directionality between the observed results (causality cannot be established in such a study). We observed that Aβ-independent age-related tau-PET uptake in parietal regions was associated with lower regional thickness, suggesting tau pathology in aging beyond the MTL, as well as its clinical relevance (*paper III*). Yet, a longitudinal characterization of cognitively unimpaired individuals that are Aβ-negative but accumulate tau is relevant to understand their atrophy patterns over time and gain insights on whether this reflects normal aging, PART, or Alzheimer's disease. This would require detailed characterization of these individuals in terms of tau-PET accumulation, other pathological biomarkers, such as Aβ pathology, progression to potential cognitive impairment, and MRI-based measures of atrophy to understand which regions are primarily affected. Ultimately, the controversy around PART and whether it is an entity independent of Alzheimer's disease [22, 29, 58, 80] can only be achieved by using a translational approach combining postmortem and longitudinal in vivo investigations of PART cases. Importantly, the length of follow-up of these investigations should be carefully considered as a slower progression has been described for PART [55]. Thus, short follow-up intervals may not be enough to capture potential changes, as highlighted by [55]. Nevertheless, our study underscores the necessity to investigate tau pathology not only in combination with Aβ pathology but also in isolation. The reasoning on longitudinal study design also applies to *paper IV*, as longitudinal studies are essential to understand if the patterns of associations can be causally linked to cognitive decline in specific-subdomains and in later stages of tau accumulation. Additionally, longitudinal follow-up studies of *paper II – part 2* would allow characterization of amnestic early-onset Alzheimer's disease, in comparison with late-onset Alzheimer's disease, in terms of atrophy patterns, changes biomarker levels, and potential steeper cognitive decline. This will further contribute to understanding if early-onset versus late-onset amnestic Alzheimer's disease represent distinct groups, increasing the insights of these two presentations also with regards to disease mechanisms, and potentially guiding enrollment in clinical trials of disease modifying therapies.

MTL subregion characterization for precision medicine

The points put forward in the previous paragraphs are important when considering that the field is aiming to move to a precision medicine approach [12, 40], allowing individualized prediction of risk, *progression*, and ultimately treatment. First, quantifying early neurodegenerative changes in MTL subregions offers predictive utility for progression of decline, as it is closely linked to cognitive changes [e.g., 311]. Second, fine-grained neuroimaging of MTL subregional atrophy allows to map the differential effects of neurodegenerative pathologies, yielding valuable insights into disease mechanisms of (co-)pathologies. For example, TDP-43 pathology has a significant impact on the clinical Alzheimer's disease trajectory [140, 155], and affects, compared to NFT pathology, different MTL subregions

(*paper V*). Quantifying subregional atrophy patterns may, thus, suggest the presence of concomitant pathologies, such as TDP-43 [e.g., 178]. This may enable the use of granular MTL differences as MRI-based biomarkers of TDP-43 pathology[1], until molecular biomarkers for TDP-43 become available [e.g., 47]. These are two examples, for which granular characterization of MTL subregions adds information allowing a precision medicine approach by offering valuable diagnostic and prognostic information and facilitating risk-benefit assessment of receiving disease-modifying treatments for Alzheimer's disease and co-pathologies, such as TDP-43.

While detailed MTL subregion characterization is very useful for precision medicine, this information alone is insufficient. To understand individual progression, it requires the integration of various sources of information. First, it requires multimodal approaches. In addition to subregional MTL structural measures and reliable Alzheimer's disease-related biomarkers, incorporating additional co-pathology data, beyond TDP-43, is essential, as the presence of one or more co-pathology may alter cognitive decline risk and progression [6, 140, 155]. Of importance is, thus, the continued development of biomarkers of co-pathologies. Proteomics and genomics, increasingly accessible through advanced platforms [285], may offer valuable additional information. Second, heterogeneity requires careful consideration as it underscores the need for personalized approaches. Heterogeneity includes factors such as diverging disease presentation [e.g., 18, 287] as well as other individual level differences, such as sex differences [e.g., 57]. To achieve precision medicine, large-scale studies integrating multiple variables and existing cohorts are required. These aspects, including but not limited to fine-grained MTL characterizations, are essential for advancing individualized patient care.

Structural neuroimaging in the era of fluid biomarkers

The points discussed above also connect to a broader question about the relevance of structural neuroimaging in the era of fluid biomarkers, specifically plasma biomarkers. Both fluid and PET markers allow to establish the presence of a disease based on the information they provide. Fluid biomarkers are valuable for screening of the aging population and increase accessibility to diagnosis and potentially prognosis [113]. Yet, no spatial information about where a given pathology occurs is provided and fluid biomarkers can be affected by non-neurodegenerative processes, such as BMI [160]. In order to obtain spatial information on pathologies,

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1 Note that such a biomarker is of relevance for investigating Alzheimer's disease co-pathologies but is of general importance for entities such as limbic-predominant age-related TDP-43 encephalopathy (LATE, [54, 306]) as well as for fronto-temporal lobar degeneration [103, 209], among others. Furthermore, this is also relevant for in vivo assessment of PART [58], where the interplay between tau and TDP-43 cannot be neglected [31, 153].

PET is still required. Due to this, fluid markers alone are not sufficient to understand and investigate disease mechanisms. This provides support for the importance of neuroimaging in general. In addition, specifically structural MRI, primarily in early stages and atypical presentations will likely continue to be crucial for several reasons. First, structural neuroimaging is required to understand spatial neurodegenerative effects on brain structure. Second, structural neuroimaging of granular regions will continue to be relevant to characterize the effects of co-pathologies on specific regions in the brain. Further advancements in MRI measures will likely results in MRI-based biomarkers of co-pathologies, such as done for TDP-43 in *paper II – part 2*, until other molecular biomarkers become available. Third, prognosis will likely include granular structural MRI measures to enable valid predictions of progression, since information about regional vulnerability cannot be detected in vivo with peripheral or omics metrics, yet. Additionally, neurodegeneration is closely linked to cognition and other clinical functions [21, 163], making MRI-based information valuable. Finally, fluid biomarkers are not able to capture heterogeneity in neurodegeneration or accumulation of pathologies in the same way as different neuroimaging measures. Thus, MRI methods, such as the ones utilized in this thesis, will remain of importance in the field of Alzheimer's disease and further contribute to our understanding of subtle and fine-grained changes and their implications, particularly at earlier (preclinical) stages and atypical presentations of Alzheimer's disease. Fluid biomarkers, PET, and structural neuroimaging markers should, thus, be used in a complementary manner, as also discussed for a precision medicine approach, where the optimal combination of biomarkers depends on the setting.

Implications for clinical trials of disease-modifying treatments

The keywords repeatedly used throughout this discussion (*subtle*, *fine-grained/granular*, *progression*) should also be considered in the context of the promising recent advancements regarding disease-modifying treatment for Alzheimer's disease [60]. At the time this thesis is written (March 2025), two treatments are available in some parts of the world: Lecanemab [81] and Donanemab [257]. General implications of these (but also prior failed) clinical trials lead to the understanding that while the removal of Aβ plaques is possible, clinical effects are limited for more advanced stages of the disease [32]. This led clinical trials to enroll earlier stages of Alzheimer's disease, ideally participants with limited tau pathology [32]. In these earlier stages, fine-grained measures from cognition and MRI could be important for both stratification and monitoring of treatment effects in the context of preclinical trials where typically used outcome measures will likely not be sensitive enough. Understanding the heterogeneity of the initial downstream effects of Aβ and tau accumulation is crucial for accurately mapping the natural progression of AD. For example, not all cognitively unimpaired Aβ+ individuals

will necessarily develop Alzheimer's disease dementia [214]. Thus, better understanding of *progression* of subtle changes is required.

In the past, larger measures of neurodegeneration, such as total hippocampal volume, have been used as secondary trial outcomes [e.g., 257]. Yet, given the additional information the measurement of MTL subregions provides, previously used secondary endpoint measures were likely too coarse to capture subtle changes over the course of a trial. While the investigation of subregional MTL measures provides more granular information, microstructural changes within the MTL may prove to be even more valid secondary endpoints. As discussed above, this requires further examination. In this context also the isolation of cognitive subdomains is of relevance, as it may allow a more fine-grained tracking of treatment responses. This is of importance as such treatment responses can be expected to be more subtle when enrolled patients are in earlier stages of the disease. Highlighted by the work in this thesis, the subregional differences within the MTL at structural and microstructural levels likely harbor a basis for more granular secondary outcome measures in clinical trials, allowing to monitor treatment responses and elucidate disease mechanisms more reliably and sensitively.

Methodological considerations

Alongside previously mentioned points (e.g., longitudinal investigations), further methodological considerations must be addressed. Selection bias is inherent to observational studies, where participants tend to be different from individuals who do not enroll in studies [325]. This may limit the generalizability of findings to other groups. In this thesis, for example, most cohorts included white and highly educated individuals. Thus, future research should investigate whether these findings extend to more diverse populations, including those with varying geographics, socioeconomic, and racial background. These considerations apply to all papers of this thesis.

Another bias may be introduced in the studies that utilized segmentation methods of MTL subregions. Individuals with cognitive impairment may have more difficulties laying still during the MRI and PET scans than cognitively unimpaired individuals. Thus, image quality can be lower, and more segmentations are likely to be excluded in the quality control process, potentially introduction a bias against more advanced disease stages.

As discussed, *paper I* is the foundation for a harmonized segmentation protocol for the MTL cortex since currently existing protocols typically do not integrate neuroanatomical parcellations by different neuroanatomical laboratories. The MTL segmentation package ASHS, which was used in the clinical studies of this thesis, is based on the information of one neuroanatomist primarily but utilized additional

neuroanatomical reference material (comprehensive mapping of one whole brain specimen) to inform the segmentation protocol [27]. Yet, several different neuroanatomists were not consulted for the protocol development. While this does not negate the utility and biological accuracy of this segmentation package, this should be kept in mind when interpreting the results of *papers II-IV*. A similar line of reasoning, can be applied to the segmentation protocol developed in *paper II*. This protocol was based on several neuroanatomical reference materials and was, thus, integrating different sources of neuroanatomical information. Yet, given the information from *paper I*, if the same specimen in each atlas would have been demarcated by several neuroanatomists, they may have shown differences, which would maybe have led to a slightly different segmentation protocol. While it is important to be aware of this potential caveat, most of the boundaries of the amygdala segmentation protocol are visible on the MR scans. However, not all borders are consistently identifiable on MRI and require heuristics. The anterior part of the segmentation protocol (i.e., the number of anterior slices excluding cortical regions) was based on the information from the neuroanatomical atlases. Due to the large heterogeneity in the human brain, the developed protocol may not be fully capturing the variability in the anterior portion of the amygdala and consequently led to under- or over-segmentation of cortical amygdala regions.

For a detailed discussions about limitations of the individual projects, see the discussions of the respective studies in the appendix.

Ethical considerations

All data utilized in this thesis originates from existing datasets or cohorts that received approval from respective ethical review boards. All study participants provided written informed consent, or for some postmortem cases, next-of-kin consent at death was given. Yet, two ethical considerations are relevant for this thesis: (i) How is the data protected to ensure the privacy of study participants ensured and (ii) Is the burden of data collection ethical for the participants?

First, data protection is ensured through several mechanisms in all cohorts. Each participant is assigned a unique study-specific number linked to their identifiable information via a separate, securely stored key. Data collection is conducted independently of the researchers who will analyse the data, preventing direct contact to the participants. Furthermore, no individual data will be published as all published data is aggregated across individuals, preventing the publication of individual-level information. All data is stored on secure servers accessible only to authorized project managers. While MR images contain some facial information that could potentially allow for identification through facial reconstruction, this is prevented

by secure data storage practices. For the ADNI cohort, the MRI core is actively investigating de-facing algorithms to further enhance anonymization [292].

Second, study participants included in the utilized cohorts provide a wealth of data obtained various methods (e.g., CSF, MRI scan, PET scan, cognitive testing, questionnaires). Even though they invest a significant amount of time and effort to this, the resulting rich datasets are used and re-used for many research projects, ultimately driving important scientific advancements.

Summary of future perspectives

To summarize, further development in measurements of MTL subregions, such as harmonization efforts, is vital to advance our understanding of disease mechanisms and establishing potential biomarkers. The inter-individual heterogeneity of the brain constitutes a challenge that may require more attention also in regions beyond the MTL. Longitudinal investigations and effects of (co-)pathologies in the here investigated contexts are required to establish directionality further.

Subtle effects on granular MTL subregions, as well as on cognitive functioning are crucial for the early detection and prognosis of Alzheimer's disease and related disorders. Additionally, the division of individuals into different phenotypes or presentations of the diseases is crucial in this context. Overall, this requires a comprehensive approach combining multiple sources of information, such as co-pathologies, to allow precise prediction, resulting in individualized precision medicine approaches. This is of relevance for clinical trials design and treatment monitoring.

Concluding remarks

Through the development of methods to measure MTL subregions in vivo and the application of studying fine-grained MTL regions, we enable the characterization of MTL atrophy in aging and Alzheimer's disease. The methodological advancements of measuring the MTL as well as the additional characterization of MTL atrophy provide a basis for developing neuroimaging biomarkers. Overall, this thesis provides a more nuanced and comprehensive characterization of the complex factors contributing to MTL atrophy in aging and Alzheimer's disease. Ultimately, this will aid in the early detection and progression of Alzheimer's disease and allow fine-grained tracking of treatment outcomes in clinical trials.

The main conclusions of the thesis are:

I. Contributions to methodological advancements for in vivo MRI measures of MTL subregions included the enhancement of our knowledge as to why differences in parcellations of cortical MTL subregions arise between neuroanatomical schools (***paper I***), and the development of a reliable in vivo amygdala segmentation protocol for MRI (***paper II – part 1***).

II. Tau pathology can occur in aging, independent of Aβ, contributing to downstream effects of neurodegeneration and cognitive decline, as shown in ***paper III***. This gives evidence for the clinical relevance of PART and highlights the necessity of investigating tau pathology in isolation from Aβ.

III. Region-specific atrophy measured with structural MRI is one pathway of tau-induced changes of different cognitive subdomains (***paper IV***), consistent with known tau spreading patterns. Moreover, isolating cognitive functions is a promising approach for future research.

IV. While subtle MTL atrophy differences exist between early- and late-onset amnestic Alzheimer's disease, the patterns are not as distinct as previously reported, suggesting a largely shared pathophysiology (***paper II – part 2***). This aids in refining our understanding of amnestic early-onset Alzheimer's disease and emphasizes the need to separate different phenotypes from each other when aiming to elucidate disease mechanisms.

V. Evidence shows that both NFTs and TDP-43 pathologies are contributing to MTL atrophy, while the mechanisms and exact interplay between the two pathologies remains elusive (***paper V***).

Acknowledgements

This thesis and its different projects would have not been possible without the generous contributions of many individuals and organizations. First and foremost, I extend my deepest gratitude to the study participants who so willingly share their time and personal information in the name of science and studying aging and dementia. Their selfless contribution is deeply appreciated.

Beyond the invaluable contribution of the study participants, I was incredibly fortunate to be surrounded by a network of supportive, inspiring, and generous individuals whose guidance and friendship were essential to the completion of this work. To each of you, I would like to offer my sincere gratitude, and I would like to specifically acknowledge:

My principal supervisor, **Laura Wisse**, for providing me the opportunity to continue my career in research and welcoming me as her PhD student. I am profoundly thankful for the invaluable scientific guidance, the broader career mentoring, and for believing in me. Your support throughout this entire process, coupled with your strong moral compass, not only brought me to this point but also give me the motivation to continue along this path. I am forever grateful!

My co-supervisor, **Nicola Spotorno**, your insightful contributions enriched all projects in some way. Your guidance in navigating the methodological intricacies of the neuroimaging field was indispensable, and I always appreciated your open ear to discuss random (scientific) thoughts. I am forever grateful for all the stimulating discussions, coffee breaks, and dinners. Your friendship is deeply valued, so I will try to reduce your cooking duties when *I invite you* over for dinner.

My co-supervisor, **Niklas Mattsson-Carlgren**, for consistently offering fresh perspectives on statistical analyses. Your insightful input and expertise have been invaluable to this work.

My co-supervisor, **Danielle van Westen**, for providing guidance and mentorship throughout these years, offering crucial encouragement and belief in me, especially during moments of self-doubt.

My honorary supervisor and mentor, **Oskar Hansson**, for sharing a portion of your vast knowledge, providing the space and support to explore this research field. You lead by example with an untiring motivation creating an incredible research

environment but also leaving room for other things (music, air hockey, sports, random ideas), reminding me to always find the fun in everything.

My mentor and friend, **Alexa Pichet Binette**, for always being there, always providing support, important insights and knowledge, and always seeing the positive! Your energy and knowledge are an inspiration. I am forever grateful for the countless ways you supported me during the PhD – far too many to list individually, but each one is deeply appreciated and will not be forgotten!

To brilliant minds behind the BioFINDER studies: **Sebastian Palmqvist**, **Erik Stomrud**, **Shorena Janelidze**, **Ruben Smith**, **Olof Strandberg**, **Pontus Tideman**, **Rik Ossenkoppele**. Your drive and expertise are an inspiration!

To the **BioFINDER study group**, who are way too many to name. Every single one has contributed to this thesis by creating an inspiring and stimulating environment allowing everyone to learn and develop. A special thank you to **Camilla Orbjörn** for your tireless dedication and for simply doing all the things you do! Additionally, to all the dedicated staff and colleagues at the **memory clinic** for working tirelessly to make the BioFINDER studies a reality and welcoming me so warmly.

To the friends I made along the way. **Nina Schultz** my frentor (friend + mentor), for your guidance, for explaining concepts of basic science, and for finding the fun in everything! Your never-ending support and reminding me of my strengths was instrumental for finishing the PhD. I would like to thank **Linda Karlsson** for the lunchtime walks, being a trusted confidant, and one of my closest friends even though you have not watched How I Met Your Mother (yet!). **Gemma Salvadó**, I am very grateful for your constant support and advice. **Anna Orduña Dolado** and **Divya Bali** thank you for your wonderful presence, ever-present smiles, and the delicious food! **Amanda Annettesdotter**, thank you for your kindness and remarkable patience in dealing with 1000 different versions of the same figure I sent. **Sophie Mastenbroek**, thank you for sharing my obsession with color schemes – it's comforting to know I am not alone. **Noëlle Warmenhoven**, thank you for the support, both emotional and in form of strategically delivered fruit platters. **Emma Coomans** and **Ellen Singleton**, I am grateful for your long-distance friendship and support throughout the last years. **Jacob Vogel**, for asking the hard questions and pushing me to believe in myself. **David Berron**, for your instrumental role, especially in the beginning of the PhD and the constant (and accurate!) reminder that cognitive assessment is fun! Finally, I am deeply grateful to **Hannah Baumeister** for coming on the incredible journey of MTL neuroanatomy together with me. All the hours on zoom reading neuroanatomy literature and writing this paper (as well as struggling with the parahippocampal cortex) taught me so much! Thank you for your patience with my constant struggle to stick to one language and your friendship along the way.

To everyone involved in the **Hippocampal Subfields Group** and specifically the Advisory Council. Additionally, I would like to thank everyone in the MTL cortex

immer bedingungslos unterstützt habt! Ein lieber Dank gilt auch **Opa Peter**, **Kirstin** und meiner ganzen Familie für die aufmunternden Worte und vielen schönen Stunden.

An meinen Bruder, **Marius**, du warst und bist eine Quelle der Kraft und Ruhe, die ich nie missen möchte! Danke dafür! Du bist mein größtes Vorbild und mein bester Freund! Ich bin außerdem dankbar dafür, dass du **Ester** in mein Leben gebracht hast – danke für all die Unterstützung und die ermutigenden Worte während dieser Zeit! An meinen Neffen **Jonah**, für die bedingungslose Liebe und die Ablenkung! Das gleiche gilt natürlich **Hilde** und meiner ersten großen Liebe, **Tobi**.

Finally, to my husband, **David**: thank you! Thank you for your unwavering support, thank you for choosing me, and thank you for being the incredible person you are! Truly, not a single page of this thesis would have been possible without you selflessly clearing my path, consistently encouraging me, and making every day brighter! Your kindness and love are my endless and constant inspiration.

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About the author

Anika Wuestefeld grew up in northern Germany, holds a Master's degree in Clinical Neuropsychology from the University of Groningen, the Netherlands, and is undergoing training to become a licensed Psychologist in Sweden.

In her doctoral thesis, Wuestefeld characterizes anatomical, methodological and clinical intrices of the medial temporal lobe in the context of aging and dementia. This thesis contributes to a more detailed characterization of the complex factors driving medial temporal lobe atrophy in these contexts, contributing to understanding of disease mechanisms which will allow fine-grained tracking of Alzheimer's disease progression and treatment outcomes in clinical trials.

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