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Retrospective application of the NIA-AA ATN scheme to patients of a German university memory clinic: role of age

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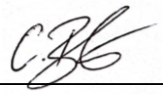
Unterschrift: 

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To my parents

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List of abbreviations

Aβ	β-Amyloid
$A\beta_{40}$	β-Amyloid 1-40
$A\beta_{42}$	β-Amyloid 1-42
AChE-I	Acetylcholine esterase inhibitor
AD	Alzheimer's Disease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Apo E	Apolipoprotein E4
APA	American Psychiatric Association
APP	Amyloid precursor protein
ATN	Amyloidpathology p-Taupathology Neurodegeneration
BDNF	Brain-derived neurotrophic factor
BNT	Boston Naming Test
BPSD	Behavioral and psychological symptoms of dementia
CA	Cornu ammonis
Ca2+	Calcium
CERAD	Consortium to establish a registry for Alzheimer's Disease
CERAD-NP	Consortium to establish a registry for Alzheimer's Disease Neuropsychological battery
CGA	Comprehensive Geriatric Assessment
CIRS	Cumulative Illness Rating Scale
CSF	Cerebral spinal fluid
DemTec	Dementia Detection
DNA	Deoxyribonucleic acid
DSM-5	Diagnostical and Statistical Manual of Mental Disorders, 5th Edition
e.g.	Exempli gratia
F	Female
FCSRT	Free and cued selective reminding test
FDG	Fluorodeoxyglucose
GCA	Global cortical atrophy
GDS	Geriatric depression scale
ICD-10	International Classification of Diseases
i.e.	Id est
IgG	Immunglobulin G
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LTD	Long-term depression
LTP	Long-term potentiation
M	Male
MCI	Mild cognitive impairment
Mg2+	Magnesium
MMSE	Mini mental state examination

MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
MTA	Medial temporal atrophy
N	Number
NCD	Neurocognitive disorders
NFT	Neurofibrillary tangles
NIA-AA	National Institute on Aging – Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMDA	N-methyl-D-aspartate
NPT	Neuropsychological testing
PET	Positron emission tomography
PKMζ	Protein kinase mzeta
PS1	Presenilin 1
PS2	Presenilin 2
p-Tau	Phosphorylate Tau protein
RNA	Ribonucleic acid
SCI	Subjective cognitive impairment
SD	Standard deviation
Sig	Significance
SP	Senile Plaques
SPECT	Single-photon emission computerized tomography
Std	Standard
TMT	Trail making test
t-Tau	Total-Tau protein
WMH	White matter hyperintensities
70-	Under 70 years old
70+	70 years and older

1. Abstract

1.1 Summary German

Hintergrund. Das Altern bringt Veränderungen in der Funktionalität, Kognition und Biopathologie mit sich, aber was ist normales Altern und was ist bereits eine Vorstufe einer schweren Krankheit. Eine große Überschneidung dieser Veränderungen mit beispielsweise der Alzheimer-Demenz erschwert die Diagnostik von älteren Patient:innen. Die Alzheimer-Krankheit stellt die häufigste Demenzform im fortgeschrittenen Alter dar und wird seit Jahrzehnten untersucht. Trotzdem sind die zugrunde liegenden ätiopathogenetischen Mechanismen noch nicht vollständig gelöst.

Zielsetzung. Es sollte untersucht werden, ob diagnostische Profile auf Basis der Klassifikation der Alzheimer-Krankheit (AD) des National Institute on Aging – Alzheimer's Association (NIA-AA) vom chronologischen Alter beeinflusst werden und im fortgeschrittenen Alter Besonderheiten insbesondere hinsichtlich der Kognition aufweisen.

Methoden. Datensätze von 222 Patienten mit kognitiven Einschränkungen, die verschiedenen ATN-Profilen zugeordnet wurden, wurden nach dem Alter der Patienten analysiert [< 70 Jahre (Gruppe 70-) und ≥ 70 Jahre (Gruppe 70+)]. Basierend auf der Zerebrospinalflüssigkeit (CSF) wurden Patienten mit Amyloidpathologie in das Alzheimer-Kontinuum (A+) eingeordnet. Das vollständige ATN-Schema wurde durch CSF-pTau- und CSF-Tau-Konzentrationen weiter beschrieben.

Ergebnisse. Ältere Patienten (76,2±4,0 Jahre, 68F, 56M) wurden signifikant häufiger als 70-Patienten (61,1±6,3 Jahre, 42F, 56M) ($p=0,018$) dem Alzheimer-Kontinuums-Profilen zugeordnet. Ein höherer Amyloidbefund war nur in der 70-Gruppe mit niedrigeren MMSE-Werten verbunden ($p<0,001$). Die Gedächtnisleistung war bei allen Patienten mit Amyloidanomalie schlechter. Die Regressionsanalyse über Alter, Amyloid, Geschlecht und GDS zeigte keine signifikanten Unterschiede im fortgeschrittenen Alter.

Fazit. Amyloidbefunde, insbesondere im fortgeschrittenen Alter, sollten die weitere Abklärung von Demenzursachen nicht einschränken, da häufig gemischte Pathologien zu finden sind und die Amyloidpathologie mit zunehmendem Alter zunimmt. Die ATN-Klassifikation könnte helfen, Patienten mit syndromaler Demenz neuropathologisch zu kategorisieren und neue Therapieansätze unterstützen. Ein spezialisierter neuropsychologischer Test scheint auch im fortgeschrittenen Alter der Schlüssel für Studien zu sein, die die Rolle der Amyloidpathologie beim kognitiven Abbau untersuchen. Andere Faktoren, die systematisch berücksichtigt werden

sollten, sind zudem solide Informationen über vaskuläre Risikofaktoren und vaskuläre Komorbiditäten, multiple Neuropathologien und mehrdimensionale geriatrische Syndrome.

1.2 Summary English

Background. Aging comes with certain changes in functionality, cognition und biopathology, but what is normal aging and what is already a pre-stage of a severe disease. A great overlap of these changes with for example dementia impedes the diagnostic of older patients.

Alzheimer's disease represents the most common form of dementia in advanced age and has been studied for decades. Despite this, the underlying etiopathogenetic mechanisms are unsolved.

Objective. To investigate, if diagnostic profiles based on the National Institute on Aging – Alzheimer's Association (NIA-AA) classification of Alzheimer's disease (AD) are influenced by chronological age and display peculiarities in advanced age especially with regard to cognition.

Methods. Datasets from 222 patients with cognitive decline allocated to different ATN profiles were analyzed according to patients' age [< 70 years of age (group 70-) and ≥ 70 years of age (group 70+)]. Based upon cerebrospinal fluid (CSF) amyloid (Aβ42) patients were classified to be within the Alzheimer's continuum (A+). The full ATN scheme was further described by CSF pTau and CSF Tau concentrations.

Results. Older patients (76.2±4.0 years, 68F, 56M) were significantly more often classified as belonging to Alzheimer's continuum profile than 70- patients (61.1±6.3 years, 42F, 56M) ($p=0.018$). A higher amyloid load was associated with lower MMSE values only in the 70- group ($p<0.001$). Memory performance was worse in all patients with amyloid abnormality. Regression analysis over age, amyloid, gender and GDS showed no significant differences in advanced age.

Conclusion. Findings of amyloid, especially in advanced age, should not limit further investigations of causes for dementia as mixed pathologies can often be found. Amyloid pathology increases with age, age-related cut-off values might clarify the pathology. The ATN classification might help to neuropathologically categorize patients with syndromic dementia and open new possibilities in the therapy. A specialized neuropsychological testing appears also in advanced age to be key in studies investigating the role of amyloid pathology in cognitive decline. Other factors that should be systematically taken into account, however, include solid information about vascular risk factors and vascular comorbidities, multiple neuropathologies and multidimensional geriatric syndromes.

2. Introduction

When reading about dementia and Alzheimer's disease (AD), almost every article starts with the discovery by Alois Alzheimer in the beginning of the 20th century [3], the unsatisfying progress of research (i.e. developing a successful treatment) [4,5] and the great burden (economic and social) of this disease [6,7] caused by the demographic development of an aging society [8,9]. All of these factors pose challenges for us as well as for future generations [6]. In 2019 worldwide costs for direct medical care and social care of dementia reached US$ 1.3 trillion [10].

The understanding and definition of dementia changed over the years. In general, dementia was often mistakenly referred to as "senility" or "senile dementia", reflecting the previously widespread false belief that mental decline is a normal consequence of aging.

Dementia is a complex heterogeneous syndrome [11] caused by age-related pathologies, which can lead independently or as mixed pathologies to a severe deterioration of cognitive abilities [12-14]. Thus, a clinically identical condition can be caused by various neuropathological mechanisms.

The several different definitions of dementia by different associations show the complexity of the subject [15] and create a problem in itself, since a clear definition has been attempted for a long time, but has not been established.

To understand why specific protein accumulations in the brain can either lead rapidly to cognitive impairment or exist in a prodromal stage of dementia without causing symptoms, research must focus on a wider view of patients including multimorbidity and medical history, social and psychological status and lifestyle behavior [16-18]. The overlap of changes caused by aging processes and dementia changes [19] poses an extra challenge in identifying the roots of pathological chain reactions that are leading to cognitive decline.

To help categorize biological variations of patients with syndromic dementia the National Institute on Aging – Alzheimer's Association (NIA-AA) research framework: "Toward a biological definition of Alzheimer's disease" introduced an ATN profile classification system, defining groups by its biological pathologies [20]: "A" describes amyloid pathology, "T" tau pathology and "N" neurodegeneration. Groups can be classified by cerebral spinal fluid (CSF) and/ or magnetic resonance imaging (MRI) [20]. The extension in the diagnostics in psychiatry from syndromes to biological defined diseases opens new possibilities in the therapy of the cause of the disease.

The ATN profiles might lead to a clearer differentiation between older and younger patients with dementia. Age is the main risk factor for dementia [21,22] and for multiple other neuropathologies including neurodegenerative diseases [23,24]. By focusing on the

neuropathology of dementia another important factor is the understanding the heterogeneous process of aging, that might lead to a better understanding of dementia and the neuropathological processes in the brain. Therefore, we examine the differences between older and younger patients of a memory clinic and compare ATN profiles and neurocognition between two age groups (< 70 years and ≥ 70 years). The cut-off age of 70 was chosen due to the explorative nature of the investigation, on the basis of previous reports [25-27]. Another goal is to see if there is a difference of the influence of pathological β-amyloid (Aβ) on cognition in both age groups.

A future aim in clinical treatment should be building a heterogeneous picture of cognitive decline in patients: going away from a one-pointed disease-orientated treatment to a preventive conscious society. Only with this paradigm change the society will be able to handle the burden of an aging society.

2.1 Burden: Prevalence and incidence

In Germany the prevalence of dementia is approximately 1.6 million people [28]. On average, around 900 new cases occur every day. They add up to more than 300,000 cases over the course of a year. [28] Worldwide more than 55 million people are living with dementia at the moment, and up to 10 million people are newly diagnosed with dementia every year [10].

Although prevalence is continuously increasing, incidence of dementia seems to stay steady or even decrease [29,30]. This effect is caused on the one hand by the demographic development of an aging society. There are more new cases than deaths among those who are already sick, and the average age is constantly increasing. Worldwide life expectancy at birth has reached 73.0 years in 2020, in Germany life expectancy at birth increased up to 81.72 years in 2020 [31]. On the other hand, the effect might be caused by the healthier lifestyle and higher education among the society [32,33]. Still if there is no breakthrough in prevention and therapy, the number of sick people in Germany will increase to 2.4 to 2.8 million by the year 2050, according to different projections of the population development. This corresponds to an average increase in the number of sufferers of 25000 to 40000 per year. [28] With over 17 years of life with disability associated with dementia [34], the current development is already and will stay a major social and economic impact in terms of medical and social care costs. “In 2019, the estimated total global societal cost of dementia was US$ 1.3 trillion, and these costs are expected to surpass US$ 2.8 trillion by 2030 as both the number of people living with dementia and care costs increase.” [10]

Diagnosed by clinical criteria 50-70% of dementia is assigned to AD and 15-25% to vascular diseases [35]. But postmortem studies show that patients with dementia show a lot more mixed pathologies and less pure AD or vascular pathologies [12,36]. These statistics show that with an

aging population dementia will become a major health issue and a challenge for society and health care [7].

Since no curable treatment was found yet, prevention strategies become more important and are already helping to stop the incidence from increasing [5,32].

2.2 Definition of dementia

Dementia, from the Latin words “de” – “out of” and “mens” – “mind”, used as an umbrella term describes a clinical syndrome diagnosed from a physician based on criteria in the definition of the syndrome in the International Classification of Diseases (ICD-10) or others without focusing on the biological cause. Therefore, we differentiate between the syndrome dementia, a specific cognitive impairment scheme in dementia caused by AD and the neurobiological pathologies of Alzheimer’s Disease, that were classified by the NIA-AA. Generally, the term dementia was often misunderstood as “senility” or “senile dementia”, representing the false belief of mental decline being part of normal aging.

There are several associations and organizations that have coined slightly different definitions, with the attempt to find a clear definition of the complex subject. Following the most common definitions are described:

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) introduced the terms of probable and possible Alzheimer’s disease: Probable AD describes progressive cognitive impairments in two or more areas of cognition with an onset of the deficits between 40 and 90 years and the absence of other diseases capable of producing a dementia syndrome. Possible AD describes an atypical cognitive impairment without a known cause. [37]

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) by the American Psychiatric Association (APA) replaced the term of dementia with the term of neurocognitive disorders (NCD). The NCD were divided into major and mild NCD. The major NCD describes a “set of existing mental disorder diagnoses from the DSM-IV, including dementia and amnestic disorder (according to the APA, you can still use the term dementia to refer to the condition). Criteria include significant cognitive decline, interference with independence, not due to delirium and not due to other mental disorder. CAVE: A major NCD can be single domain with the exception of major NCD due to Alzheimer’s disease” [15]. The mild NCD presents a “moderate cognitive decline not interfering with independence, not due to delirium, not due to other mental disorder” [15]. [38]

The International Working Group defined AD as the “presence of an appropriate clinical AD phenotype (typical or atypical) and a pathophysiological biomarker consistent with the

presence of Alzheimer's pathology such as volumetric MRI and fluorodeoxyglucose Positron emission tomography (PET)" [15]. [39]

2.2.1. ICD-10

Following symptoms must sustain for at least six months and lead to limitations in the functional activities of daily life [2].

"Dementia (ICD-10-Code: F00-F03) is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation. This syndrome occurs in Alzheimer disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain." [2]

"Dementia in Alzheimer disease (G30.-)

Alzheimer disease is a primary degenerative cerebral disease of unknown etiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years

F00.0 Dementia in Alzheimer disease with early onset (G30.0†)*

Dementia in Alzheimer disease with onset before the age of 65, with a relatively rapid deteriorating course and with marked multiple disorders of the higher cortical functions. […]

F00.1 Dementia in Alzheimer disease with late onset (G30.1†)*

Dementia in Alzheimer disease with onset after the age of 65, usually in the late 70s or thereafter, with a slow progression, and with memory impairment as the principal feature. […]

F00.2 Dementia in Alzheimer disease, atypical or mixed type (G30.8†)*

Atypical dementia, Alzheimer type

F00.9 Dementia in Alzheimer disease, unspecified (G30.9)" [2]*

2.2.2. NIA-AA Definition

Criteria of the NIA-AA are divided into general criteria to define dementia and clinical criteria to distinguish between dementia caused by AD and other forms of dementia. Thus, to get a better understanding of the disease and the ability to interpret biological markers.

General criteria for dementia are given if 1. There is a deficit in the functional activities of daily life 2. A cognitive impairment in comparison with an earlier state of cognition 3. No other explanation like delirium or another psychological disease 4. The cognitive impairment is diagnosed by a combination of auto anamnesis and indirect anamnesis and an objective neuropsychological test or a clinical cognitive test. 5. At least two of the following parts must be affected: a. Memory function b. To understand and perform complex tasks, judgment c. Spatial-visual functions d. Speech functions e. Changes in behavior ("personality changes"). [40]

Mild cognitive impairment (MCI) does not meet the criterion of limited activities of daily life due to cognitive impairment or behavior changes.

Dementia caused by AD has a specific cognitive impairment pattern with a slow start and common symptoms: a) amnestic variation (most common) – deficit of the episodic memory function especially learning and recall plus at least one more deficit in one of the domains above , b) non-amnestic variation – deficits in language presentation, visuospatial presentation or executive dysfunction. [40]

If the clinical syndrome fits the criteria for an AD typical dementia and excludes other substantial cerebral diseases like stroke, Lewy-body dementia or frontotemporal dementia, biomarkers and imaging can help to verify the biological diagnosis of Alzheimer's disease as a cause of dementia [40].

2.2.3. AD – a biological definition

Table 1: ATN classification system based on NIA-AA framework 2018 by Jack et al.
Participants are categorized based on neuropathological changes

AT(N) Profiles	Biomarker category	
A-T- (N-)	Normal AD biomarkers	
A+ T- (N-)	Alzheimer's pathologic change	Alzheimer's continuum
A+ T+ (N-)	Alzheimer's disease	
A+ T+ (N+)	Alzheimer's disease	
A+ T- (N+)	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change	
A-T+ (N-)	Non-AD pathologic change	
A-T- (N+)	Non-AD pathologic change	
A- T+ (N+)	Non-AD pathologic change	

"A: Aggregated Aβ or associated pathologic state

CSF $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio

Amyloid PET

T: Aggregated tau (neurofibrillary tangles) or associated pathologic state

CSF phosphorylated tau (p-tau)

Tau PET

(N): Neurodegeneration or neuronal injury

Anatomic MRI

Fluorodeoxyglucose (FDG) PET

CSF total tau (t-tau)" modified from [20]

2.3 Aging

The aging process is widely misunderstood as a "normal" decline in all kinds of different body functions, e.g., capacity of movement, mental functions. Therefore, ageism describes the discrimination against individuals or groups based on their age. These societal beliefs lead to poorer medical care for the elderly.[15] "Late diagnosis occurs because older patients tend to minimize their complaints, considering them part of "normal" aging, and also in part due to the concerns associated to a diagnosis of dementia—fear of limited own independence, management of finances, inheritance issues within the family, withdraw of driving licence, etc.:

• Understanding of memory impairment as normal in advanced age

• Lack of neurogeriatric education

• Ageism

• Fear of losing independence" [15]

Because of these reasons older patients often poorly communicate their problems, in this way cognitive impairment remains largely undiagnosed. This information gap created by the patient himself must be filled by the medical system, since multiple problems occur in advanced age but cannot be seen as normal aging. "From a geriatric perspective, the use of a Comprehensive Geriatric Assessment (CGA) foresees that the older person undergoes cognitive evaluation together with clinical, functional, and social examinations [41]. By systematically including cognition among the domains explored in an older adult, problems related to poor detection of cognitive impairment and late diagnosis of dementia are overcome [41]." [15]

"Despite the fact that cognition is frequently negatively affected by inadequate clinical decisions and treatment plans [42,43], it is not systematically addressed in hospitals and up to 89% of older patients with a mini-mental state examination (MMSE) <24 might have been not diagnosed with cognitive impairment at the hospital admission occurred during the previous 12 months. However, proactive care targeting cognitive impairment might be extremely effective in very vulnerable multimorbid older patients, not only with respect to health outcomes, but also regarding quality of life and well-being. In addition, when progression of cognitive impairment and dementia is ascertained, patients and caregivers—the latter usually providing the largest part of the care to the cognitively impaired person—should be systematically allowed to be central authors of important decisions regarding prognosis of dementia, advanced care planning, and palliative, legal, and ethical issues." [15]

The process of aging is complex and contains genetic and epigenetic changes in the genome that lead to structural changes in the human body. Time shows the deficiency of the repair mechanisms of the deoxyribonucleic acid (DNA), which unsuccessfully mend all telomere attrition and accumulation of mutations leading to genomic instability. Furthermore, epigenetic mechanisms (i.e. DNA methylation, histone modifications, and noncoding ribonucleic acid (RNA) species) show age-related alterations of the genome structure and function. These alterations affect parts of nuclear processes like gene transcription and silencing, DNA replication and repair, cell cycle progression, and telomere and centromere structure and function. The genetic and epigenetic progresses represent the factors of aging and therefore aging-related diseases. [44]

Neuroplastic changes in a normal aging brain and normal cognitive decline are further described in the next chapters.

2.4 Neuroplastic changes

2.4.1. Neuroplastic changes in a normal aging brain

The human body is a self-renewing system that constantly changes in structure and plasticity, in particular the brain as a high functioning and convertible organ [45]. Therefore, every learning process and interaction as well as normal aging as a process of renewing structures seems to include structural brain changes without any symptoms. A lot of these changes are overlapping in normal aging and AD thereby it is hard to differ between what is normal aging and what is a first / pre- stage of progressive degenerative condition that leads to dementia [19,24]. As a high functioning organ, the brain needs to renew more often than other organs, thus more errors will occur throughout the lifetime. It is hard to say to what extent errors can be considered as normal and at what point an unnormal aging process starts. Although normal aging is a very heterogeneous process, some neuroplastic changes could be generally found in elderly without great functional losses in everyday life: decrease of brain volume and expansion of the ventricular system, reduction of grey matter [45,46] and decrease of hippocampus size [47]. Neurofibrillary tangles (NFT), senile plaques (SP), neuronal and synaptic loss belong to normal aging as well as to AD [19] and increase with age in individuals with and without dementia [23,48-50]. Locations in the brain that are highly neuroplastic show greater vulnerability in both aging and AD [11]. Part of the cause of the shrinking brain is the loss of neurons in the prefrontal cortex [51].

Another aspect of aging is the perturbed calcium (Ca^{2+}) homeostasis and changed calcium influx [52]. The disturbed homeostasis can first be balanced by other calcium buffer systems like the mitochondria or plasmalemma. Though a long lasting high mitochondrial calcium uptake

seems to contribute to cell death. Furthermore, aging assumes to indicate the alteration of ryanoide receptor levels and the modulation of the ryanoide receptor itself, which are important for memory building. [53]

In total it seems that these age-related changes have an impact of the vulnerability for pathological neurodegenerative changes as in AD [24]. And aging as the major risk factor for AD [21,22] still needs to be more understood. How does normal brain aging affect pathological aging? And why can amyloid cause cognitive decline but exist in a stable way for decades without leading to any symptoms?

All age-related changes are presented in table 2.

Table 2: Age-related changes in the brain modified by Polidori [15]

Macroscopic	- Reduced brain weight and hippocampal volume decrease - Expansion of ventricular system - Increased white matter hyperintensities
Microscopic	- Diminished number of neurons - Diminished number of synapses - Increased deposition of β-amyloid plaques, neurofibrillary tangles and neuropil threads - Increased glial proliferation - Increased vulnerability of brainstem monoaminergic systems, basal forebrain nuclei and myelinated nerve fibers
Electrophysiologic	- Decreased α-wave rhythm at EEG
Vascular modifications	- Decreased cerebral perfusion - Amyloid angiopathy - Impaired trophic influence of microvascular endothelium - Vascular atherosclerotic burden
Cellular intrinsic and programmed changes	- Replicative senescence - Telomere shortening - Sirtuin dysregulation - Apoptosis
Cellular extrinsic and stochastic changes	- Error catastrophe and somatic mutation - DNA mutation accumulation

Cellular extrinsic and intrinsic modifications	- Wear and tear
Molecular changes	- Chaperone dysfunction and misfolded protein accumulation - Free radical production and oxidative stress - Mitochondrial dysfunction and altered energy production - Protein glycation - Inflammation - Metabolic dysregulation - Codon restriction - Genetic dysregulation - Neurotransmitter and modulator imbalance

2.4.2. Neuropathological changes in AD

Alzheimer's disease is other than dementia a biological-pathological definition that can only be surely diagnosed by post mortem examination and was first described by Alois Alzheimer [3]. The disease is characterized by histopathological cell loss, amyloid plaques and tau pathology. These changes can occur 20-30 years before the development of symptoms [54]. Under 5% of all AD cases belong to the dominantly inherited forms of AD with a clear genetic component, the rest occurs sporadically and is part of the non-dominant forms [55]. For the dominantly inherited forms mutations on three genes are known, the gene for the amyloid precursor protein (APP) on chromosome 21, the genes presenilin 1 (PS1) on chromosome 14 and presenilin 2 (PS2) on chromosome 1 [55,56]. The defined changes are characterized by positive lesions: amyloid plaques, cerebral amyloid angiopathy, NFT and glial responses and negative lesions like neuronal and synaptic loss [57].

AD runs in stages of amyloid and tau pathology [18]. The accumulation of amyloid runs in 5 phases. The initial stage shows amyloid deposits only in the neocortex. Following that amyloid can be found additionally in the allocortical brain regions (including the hippocampus and the olfactory system). Followed by the diencephalic nuclei, the striatum and the cholinergic nuclei of the basal forebrain in phase 3. In stage 4 further amyloid aggregates deposit in various brainstem nuclei. Finally, amyloid deposition is found in the cerebellum in phase 5. Phases 3,4 and 5 seem to contribute to AD, whether 1, 2 and 3 are also found in nondemented cases and represent precursors. [18]

Aβ is a protein, that is build up after the sequential cleavage of the transmembrane APP by the β- and γ-secretases into a 40 or 42 amino acid peptide. The amyloid hypothesis describes amongst other things an imbalance between APP and chaperones, proteins like the apolipoprotein E4 (apo E), which are part of the dismantling of the peptides [56]. Thus, depending on the allele constellation (heterozygous 45% and homozygous 10-12% of all Alzheimer's patients), the apo E gene is a risk factor for the development of AD, whereby the apo E in particular is associated with a significant increase in risk [55]. The imbalance described above leads to an increase of the poorly soluble peptides, amyloid β1-42 ($A\beta_{42}$) and -40 ($A\beta_{40}$), which accumulate and form synaptotoxic and insoluble amyloid fibrils, the main constituent of amyloid plaques (mainly $A\beta_{42}$) and cerebral amyloid angiopathy (mainly $A\beta_{40}$) [18,57,58]. These plaques are extracellular and can be classified into dense-core, diffuse plaques and neuritic plaques. Dense-core plaques are associated with synaptic loss, dystrophic neurites (neuritic plaques), reactive astrocytes and activated microglial cells, and probably contribute to cognitive impairment [57]. On the other hand diffuse plaques can be found in elderly without cognitive decline and are not associated with neuronal, synaptic loss or cognitive impairment [57]. Moreover, amyloid plaques provoke an activation of microglia cells which initiates a proinflammatory response with ejection of neurotoxic molecules, thus a progression of pathological change [56,59]. All in all, different amyloid aggregations contribute in various ways to synaptic dysfunction and neurodegeneration and are topic of current research [60].

Another part of the pathology is based up on tau protein. Neurofibrillary tangles as staged in Braak and Braak 1991 are proteins, which phosphorylate intraneuronal and misfold into aggregates that cause the death of the neuron whereby the hyperphosphorylated tau becomes extraneuronal.

In the initial stage of AD neurofibrillary tangles can be found in the limbic system in the transentorhinal cortex – corresponding to Braak and Braak stages 1-2. From here NFT spread from transentorhinal regions to the entorhinal cortex (stages 3-4) and to the allocortex and isocortex [61]. In contrast to normal brain aging cornu ammonis (CA) 1 and CA 2 regions of the hippocampus and pyramidal cells are mainly damaged [19]. These regions with characteristic high neuroplastic long axonal connections are especially vulnerable to AD [11,62]. All these regions are part of the medial temporal lobe, which shows a reduction of volume in AD [63].

Neuropil threads accompany NFTs and are aggregated and hyperphosphorylated tau proteins in axonal and dendritic segments.

Tau protein in general is a microtubule-associated protein close to the axon, stabilizing and binding microtubules to facilitate the axonal transport. [57]. Thus, aggregated NFTs lead to instability of axonal transport and cell death.

Apart from these characteristic pathologies of AD, further pathological changes could be found in the last decades for example lower levels of magnesium (Mg^{2+}) and calcium. The calcium hypothesis tries to link the amyloid pathology to the dysregulation of cellular calcium homeostasis and cognitive decline: Amyloid β influences Ca^{2+} levels and APP alters ryanoide receptors. Both are needed in the process of long-term potentiation (LTP), which is part of learning and memory development. The interaction of the amyloid pathway leads to a remodeling of the calcium signaling system which contributes to cognitive impairment and neuronal cell death. Synaptic plasticity and the strength of central glutamatergic synapses are highly depending on increased or decreased calcium levels, which distribution plays an important role in cognition processes. [64-66]

Another mineral that plays an important role in LTP is magnesium. Mg^{2+} needs to bind together with glutamate to the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to strengthen synapses. Lower levels of magnesium could be found in AD. [67-70]. Magnesium intake appears to have a preventive effect of cognitive impairment. [71]

Moreover, studies indicate pathological changes in the monoamine system, especially in the serotonergic and noradrenergic system. Reduction of serotonin, loss of noradrenergic neurons and decreased levels of dopamine, histamine and melatonin assume to contribute to disturbances in the sleep-wake cycle and the behavioral and psychological symptoms of dementia (BPSD). [72]

2.4.3. Neuropathological changes leading to dementia

Dementia is a clinical diagnosis that can be caused by numerous age-related neuropathologies as well as a mix out of these ones [14]. In the newest study just 1/3 cases were caused by Alzheimer's disease, which makes AD still the strongest driver of dementia though it is less than previously thought. Most common was a mixed pathology. [12]. Other causes that lead to dementia were macroscopic infarcts, Lewy bodies, hippocampal sclerosis, limbic-predominant age-related TDP-43 encephalopathy (LATE), cerebral amyloid angiopathy, atherosclerosis and arteriosclerosis. [12-14,36]

2.5 Diagnostics

According to German S-3-guidelines dementia is a clinical diagnosis, supported and specified by imaging and CSF diagnostics [73]. After a detailed anamnesis (auto and indirect anamnesis) with special focus on drugs and risk factors, and a physical examination, an initial etiological assignment and an assessment of the severity should be made. For an orientation assessment of the cognitive impairment short tests should be used like MMSE, dementia detection

(DemTec) or Montreal cognitive assessment (MoCA) [74-77]. Furthermore, neuropsychological testing should be used to clarify the etiology and give a better classification in severity [78].
Common diagnostical methods, neuropsychological testing (NPT), MRI, CSF, are currently used will be presented further. New technologies (PET, single-photon emission computerized tomography (SPECT), blood tests) are already used in research and memory clinics leading to more specific diagnostics and help to get a deeper understanding of the disease and will become an important part in the future. Studies show that sensitivity and specificity increase with age adjusted automated analysis in FDG-PET [79].
Diagnostic accuracy is important for the specific treatment. Acetylcholine esterase inhibitors (AChE-I) and NMDA modulators are only effective if AD is part of the cause for the cognitive decline [80], but have side effects that should be considered especially for older patients [60].

2.5.1. Neuropsychology

To get a differentiated picture of the patients a neuropsychological testing is important in the diagnostic. A cognitive performance/ impairment profile can be generated age-, gender- and education-related and depressive symptoms can be detected. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) is a battery of standardized tests to define the cognitive domains of a patient including verbal fluency, Boston naming test (BNT), MMSE, word list learning, word list recall, drawing figures, figures recall, phonematic fluency, trail making test (TMT) A, B, A/B, Free and cued selective reminding test (FCSRT) [81,82]. Each test reflects different cognitive dimensions and therefore represents different locations of the brain (Table 3) [83,84]. Scale values are standardized in consideration of age, gender and education and compared based on validated standard values for each individual although the total variety can't be totally represented.

Table 3: Neuropsychological tests, their dimensions and corresponding brain regions

Test	**Dimension**	**Brain region**
MMSE	Multiple dimensions	Multiple locations
Boston Naming Test	Language	Dominant hemisphere, neocortical frontotemporoparietal areas
Semantic Fluency	Categorical fluency	
Phonematic Fluency	Phonematic fluency	
Word List Learning	Learning	Mesial temporal lobes, Medial thalamus, basal forebrain, and
Word List Recall	Recall and memory	

FCSRT Free Recall	Recall and memory	other elements of Papez's circuit (hippocampus)
FCSRT Total Recall	Memory	
Figures Recall	Visuospatial recall Vision	Parieto-occipital
Drawing Figures	Visuospatial function	Non-dominant hemisphere, parietal lobe
Trail Making Test A	Visuoconstruction Attention	Frontal ± temporal lobes and subcortical connections
Trail Making Test B	Executive function	Frontal ± temporal lobes and subcortical connections

2.5.2. Cerebral spinal fluid

One way to specify the causes of cognitive impairment is to examine cerebral spinal fluid. In 9% of the cases a reversible cause can be found and treated [73]. Therefore, standard biomarkers are examined. According to the German S3-guidelines cell number, total protein, lactate concentration, glucose, albumin quotient, intrathecal immunglobuline G production and oligoclonal bands should be part of every CSF analysis to exclude diseases like viral encephalitis, lues, Whipple's disease, neuroborreliosis, neurosarcoidosis, multiple sclerosis and brain abscess.

Furthermore, neurodegenerative diseases can be diagnosed by combination of CSF biomarkers and clinical symptoms, especially probable AD. These biomarkers are a correlation for the pathological changes in the brain. Important biomarkers are $A\beta_{42}$, t-tau, p-tau. A low $A\beta_{42}$ indicates presumable the amyloid plaque accumulation in the brain [26]. These plaques were found post mortem in patients with AD [85]. For an increase of evidence use of the $A\beta_{42}/A\beta_{40}$ ratio in addition to the usual CSF AD biomarkers is recommended [86] using $A\beta_{40}$ as a marker for general amyloid production. Tau protein belongs to the microtubule-associated proteins intraneuronal and contributes mainly to the operability of the cytoskeleton. Caused by a "hyperphosphorylation" of the tau protein (phosphorylated = p-tau) it forms fibrils and loses its functionality which causes destruction of the cytoskeleton and the leakage of the protein into the cerebrospinal fluid and thus a increased t- and p-tau [26].

For a proper interpretation of CSF biomarkers following aspects need to be taken into consideration: A combination of all CSF biomarkers has the highest sensitivity and specificity and can help to clarify a diagnosis. CSF biomarkers alone cannot be used to differentiate

between neuropathological diseases: A negative amyloid indicates a cause other than AD [87]. A positive biomarker can be the cause of the cognitive impairment (i.e. AD) [88], but is also found in 30% of cognitive healthy older adults (i.e. pre-stage of AD [89,90] or aging pathology) [91]. Furthermore, older adults are more multimorbid and have more illnesses that can lead to a cognitive decline. Thus, specificity decreases with age [26,88,91].

2.5.3. Magnet resonance imaging

The MRI can support the clinical diagnosis of dementia [40]. It can identify treatable illness (e.g. normal pressure hydrocephalus, neoplastic changes) and depict AD typical structural changes of the hippocampus, mesial temporal lobe, the white matter and global cortex, which are prominently found post mortem [63,92,93]. To objectify the changes scales are generally applied. The medial temporal atrophy (MTA) scale describes the medial temporal lobe and the hippocampus in three ways: width of the choroid fissure, width of the temporal horn of the lateral ventricle and height of the hippocampus [63]. White matter hyperintensities (WMH) appear from small vessel diseases due to aging or neurodegeneration [94]. Correlations between periventricular WMH and demyelination and axonal degeneration could be found [95]. WMH can be classified with the Fazekas score describing periventricular hyperintensities and deep white-matter hyperintensities [96]. The global cortical atrophy (GCA) scale, first described by Pasquier [97], graduates cerebral atrophy on basis of measurement of sulcal and ventricular dilatation of different brain regions [98].

All findings should be fully described and additionally objectified as a scale number. Results must be put in relation to clinically suspected diagnosis and other examinations [98].
Because of the overlapping histopathologic changes between AD and aging, age-specific interpretation shows a more accurate link between visual ratings and diagnosis [99-101]. Future age-based scales should be considered.

2.6 Therapy

The therapy of dementia combines several different facets including psychoeducation, medical treatment of the cognitive impairment, treatment of somatic diseases, therapy of behavioral problems and treatments that focus on the maintenance of daily functions (Figure 1) [102].

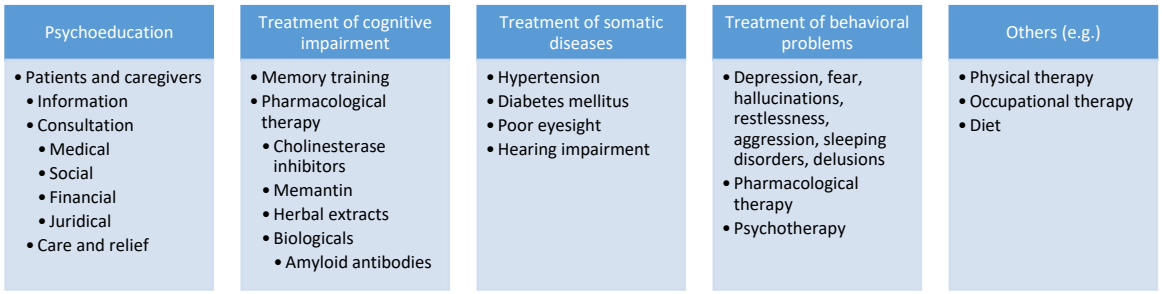

Figure 1: Multimodal therapy concept for dementia mod. L. Frölich 2021[102]

Since no cure was found yet, the treatment of modifiable risk factors as hypertension or diabetes plays an important role and has a preventive effect on cognitive decline and dementia [103]. Prevention itself will become a key role in the future. By reducing the number of new cases by treating molecular disease processes or by reducing risk factors before the symptoms develop, the increasing number of dementia cases might be reduced. Especially in the case of AD, both early detection and probably effective prevention are possible due to successful research on biomarkers, molecular therapy approaches and lifestyle-based risk factors. [104]

Psychoeducation, psychotherapy, memory training and physical activities help to maintenance the level of functions in the daily living [102,105].

The symptomatic pharmacological therapy is based on AChE-I (Galantamin, Donepezil, Rivastigmin) or NMDA receptor-antagonist (Memantine). AChE-I are used in mild to moderate dementia caused by AD. They increase the functional activity of the cholinergic neurotransmitter system in the central and autonomic nervous system.
The NMDA antagonist Memantine is used in moderate to severe dementia. Memantine is a voltage-dependent low-affinity glutamate modulator, that protects the neurons from excessive glutamate flooding without impairing glutamate-mediated memory processes.
A combination of both drugs can be used. [102]

Because of the amyloid-hypothesis a new attack point for drugs was amyloid. New biologica – amyloid antibodies with different targets in the amino acid sequence were tested in studies.

Aducanumab showed significant biological effects i.e. a significant reduction of Aβ in the brain measured by PET scan, so that the food and drug administration in the United States of America gave admission through the accelerated pathway for this biologica [106]. Aducanumab

can be used in the treatment of patients with an early state of AD, but has some severe side effects and need regular MRI checks.[107]
More amyloid antibodies are in clinical trials and might be getting an approval in the future (e.g. Lecanemab, Gantenerumab) [108].

The concept of disease-modified therapy in Alzheimer's disease aims at the pre-dementia stages with biomarkers as a diagnostic basis. The mechanisms focus on the proteinopathies (amyloid and tau). Anti-tau approaches are still in the research phase. Further drug studies are with repurposed drugs like Metformin. Therapy with combinations of the above ones are expected. Despite these future therapy options, a large number of Alzheimer's patients do not meet the therapy criteria for the biologica, so that prevention strategies continue to represent an important pillar of therapy. [109]

2.7 Learning and memory

Learning is a process that starts even before we are born and that changes our behavior through the experiences we get from the interaction with our surroundings. These experiences are preserved in the networks of neurons in the brain and can be retrieved to influence our behavior. Furthermore, the connections between these neurons are modified by the impact of our experiences leading to what it is called synaptic plasticity [110]. A memory is the capture and retrieving of these past experiences and the reuse of the built linked network of neurons. Whether learning nor memory are singular consistent processes. [1]
The ability of learning and recalling memory decreases in dementia as well as in the spectrum of age-related cognitive decline.
Learning and memory are still not fully understood, since memories are difficult to be observed. Further understanding of the biological ways of preserving information might help to understand why these cognitive areas are hit early in cognitive impairment. This chapter is a simplification of the current state of research.

Experience is information that we take from the environment, this sensory information is first processed in cortex regions, depending on the sensory stimulus. Each area can transmit signals to other brain regions for further processing. In order to be able to store information over a longer period, various structures play an important role, especially the medial temporal lobe with the hippocampus, amygdala and as cortical areas, the entorhinal and perirhinal cortex as well as the parahippocampal cortex. The diencephalon and the basal forebrain play another, yet unknown key role in memory building. Permanent storage is reinforced by repetitions and links to existing knowledge. In addition, the type of information processing, the degree of correspondence between encoding conditions and retrieval conditions and the

number of clues available to trigger a retrieval are important. To learn is a physical change in the neuronal network. There are many possible ways of change like the way the neurons fire, the form and size, the number of connections between neurons and new protein synthesis. [1,111]

Current theories divide the mind into different kind of memories: the long-term memory is a storage of knowledge and records of previous events that can be recalled for a long time. The short-term memory gives the access to hold a limited amount of information temporarily in a conscious and unconscious way. Thus, short-term memory differs from long-term memory in duration and capacity. The working memory is used to plan and carry out our behavior. [112]
Experiences can produce memory traces by activation of cellular-molecular processes, which in turn are influenced by neuronal and hormonal processes that are activated by emotional arousal and therefore are memory modulators. [113] It assumes that experiences can quickly form a short-term memory trace that can evolve into a long-term memory. [111] There are several aspects found that help to remember things longer: repetition, primacy and recency, surprise, emotional impact and the lead to a positive or negative outcome. Fear for example is a strong memory modulator that activates neurons in the amygdala, hippocampus and cortex. Even after several weeks after learning something in fear the degree of reactivation in the cortex remains stable. [114]

Learning and making memories can be structured into three steps: I. encoding, II. consolidation and III. recall / recognition. For a short-term memory encoding preexisting protein change and modify preexisting synaptic connections. But there is no consolidation happening. To build a long-term memory the activation of gene expression leads to new protein synthesis and new synaptic connections. [1,115] The binding of glutamate to NMDA and AMPA receptors in the synapse can lead to synaptic changes that support long-term potentiation. A neuron that often activates another neuron strengthen the synaptic connection [116]. LTP is the effective connection between neurons, that happens after repetitive learning in neurons. In normal synaptic transmission an incoming action potential in the presynapse causes the release of neurotransmitters - here glutamate - into the synaptic cleft. Glutamate activates AMPA receptors in the postsynaptic membrane. Thereupon sodium ions flow into the cell, so that it depolarizes, and a new action potential arises. The depolarization releases magnesium ions from the NMDA receptors. If a new action potential arrives in the presynapse at the same time and glutamate is released again, it activates both the AMPA and the NMDA receptors. This can release a large amount of calcium to flow in. Leading to more AMPA receptors being built into the postsynaptic membrane. In the long run, this increases the transmission strength of the synapse. [115]

In contrast, long-term depression (LTD) is a mechanism that helps us to forget. It is triggered when nerve fibers in the hippocampus are stimulated with a low frequency of one to five hertz for a longer period of time or when nerve cells that communicate with each other are stimulated at different times. As a result, fewer neurotransmitters (i.e. glutamate) flow into the synaptic cleft and less calcium gets into the post-synapse. As a result, the number of AMPA receptors in the post-synapse decreases and the pre- and post-synapse shrink. In the future, it is less likely that the two neurons will be stimulated at the same time. [117]
The amount of calcium that enters the postsynaptic cleft is decisive for both processes. While a strong influx of Ca^{2+} through the NMDA receptor leads to LTP, a low Ca^{2+} inflow leads to LTD. [111]

Short-lasting LTP is supported by post-translation processes, while long-lasting LTP requires transcription and translation processes to produces new proteins and connections. The induction of LTP is fast, but the consolidation requires a sufficient induction stimulus, leading to the presynaptic release of both glutamate and brain-derived neurotrophic factor (BDNF). Consolidation processes happen in several waves for at least 24 hours. Deep sleep seems to support this process through a reactivation of the hippocampus and a hippocampal-neocortical dialogue. [118] After this process the memory trace goes from an unstable vulnerable trace to a stable consolidation. To maintain this consolidation over time molecular processes must operate continuously leading to unknown processes in which protein kinase mzeta (PKMζ) probably plays an important role. [119,120]

The areas with glutamatergic synapses are especially present in the cerebral cortex, the amygdala, the cerebellum and in the hippocampus. It was found that different attributes are connected to different regions of the brain for storage. Semantic memory is stored in the cerebral cortex, episodic memory in the hippocampus and procedurally skills in the cerebellum and basal ganglia (Figure 2: Long-term memory) [1,111].

All in all, learning and memory building are complex processes which need specific conditions like good electrolyte balance and deep sleep, which often decreases with age.

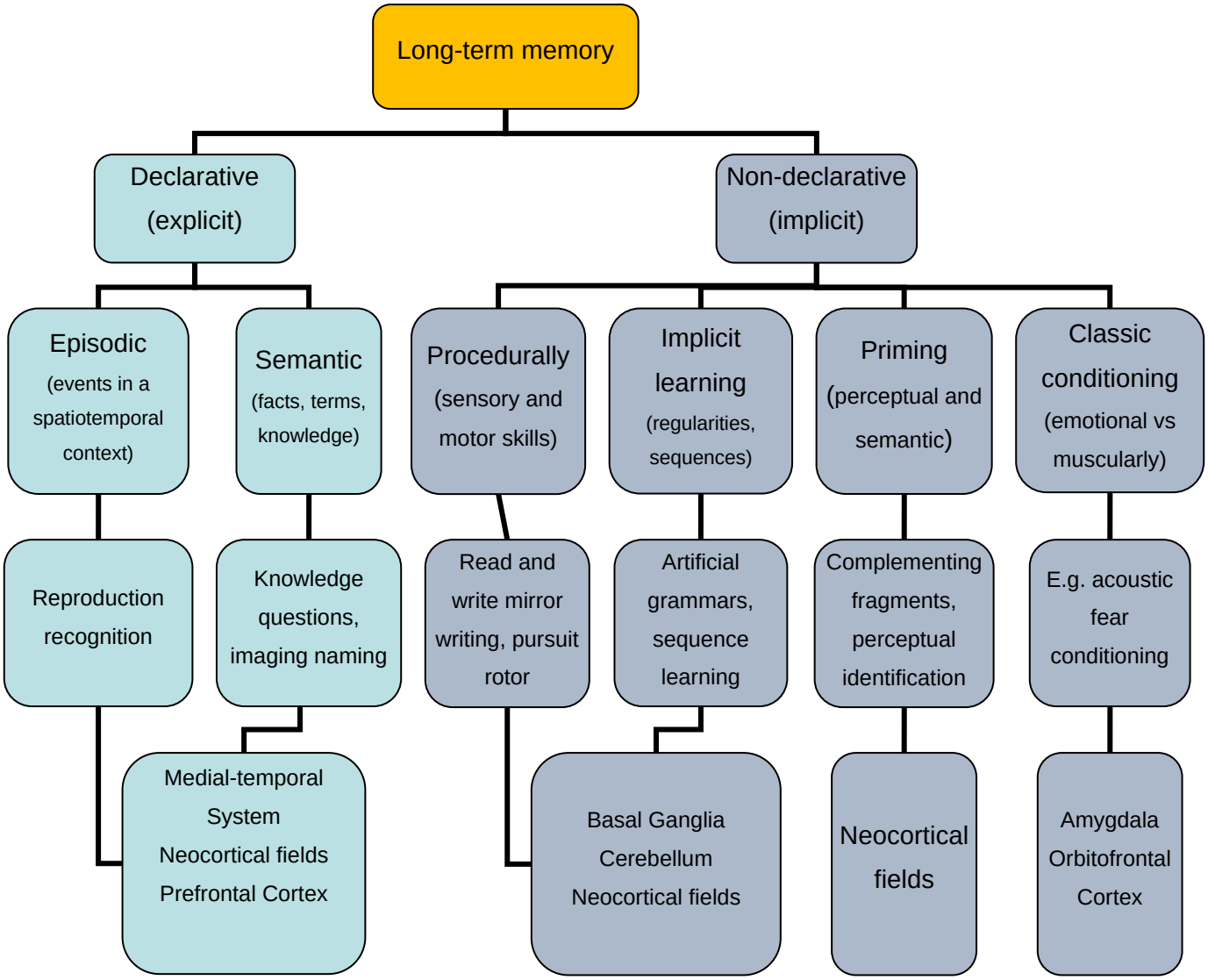

Figure 2: Long-term memory modified from Gluck [1]

2.7.1. The importance of forgetting

While talking about forgetting, we mostly think about a passive and negative afflicted process with loss of memories or memory traces but forget that forgetting is much more than that. In addition to the passive process, there are also active processes that promote forgetting. Active forgetting is important for abstract thinking, creative problem solving and focusing on the essential, thus for the increase of information processing speed. Furthermore, it helps to update information and separate important and unimportant information of daily life. Unnecessary memories are erased systematically mostly in the sleep [121]. How well we can memorize relates to how well we can forget.

Figure 3 shows different forms of forgetting separated into passive and active forgetting: Impeded retrieval, biological decay and time, motivated forgetting, retrieval-induced forgetting,

intrinsic forgetting, interference-based forgetting are the major forms of forgetting postulated by scientist.

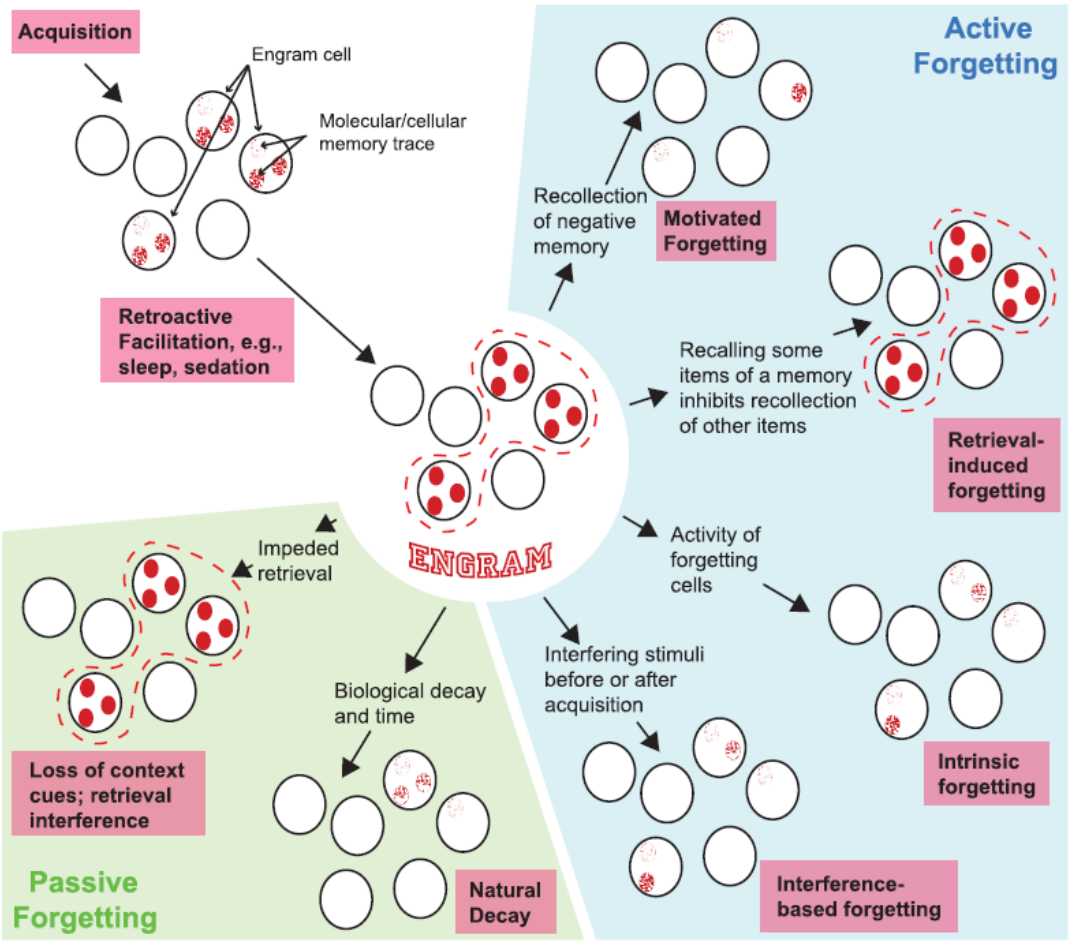

Figure 3: Engram, i.e. trace of a stimulus left in the central nervous system and forgetting [122]

Interference-based forgetting is a theory that competing stimuli before (proactive) or after (retroactive) acquisition change the memory by acceleration of the decay of the old memory traces, e.g. getting a new telephone number or a friend has a new address [123-126].

Motivated forgetting shows an increasing activation in the dorsolateral prefrontal Cortex which is associated with control processes and a lower activation in the hippocampus which is associated with long-term memory. Motivated forgetting can be compared with Freud's term of repression using retrieval suppression of the memory to mostly repress unpleasant events. [127-129]

Retrieval-induced forgetting *"occurs when some aspects of a memory are recalled that suppress the recall of other aspects related to the recalled memory. This type of forgetting may disrupt the retrieval of a relatively intact memory engram."* [121]

Intrinsic forgetting is a new form of active forgetting involving the activity of forgetting cells that release dopamine onto engram cells. This leads to an activation of Rac1/ Cofilin which changes

the actin cytoskeleton and therefore the neuron and synapse structure. Thus, a molecular and cellular degradation of the memory traces. [121]
Forgetting is an important part for an independent daily life, as long as it does not start to impair the normal daily activities.

2.7.2. Age-related cognitive decline

In the heterogeneous aging process cognitive decline plays a big part in the continuum between healthy aging and dementia. Cognitive decline can be described as a multifactorial geriatric syndrome [15] with decrease of different cognitive domains. These impairments are overlapping with dementia. Cognitive functions were historically grouped into crystallized and fluid intelligence. Crystallized intelligence are mostly stable functions like over-learned (vocabulary, information, comprehension, arithmetic) and well-practiced, familiar skills, ability or knowledge [130]. Fluid intelligence is characterized by a slow decline until the late 50ths or early 60ths after that the decline increases rapidly (i.e. reasoning and problem solving) [131]. Age-related declines are found in episodic and working memory [132,133], as well as immediate memory [134] and verbal and non-verbal memory [135], processing information speed, executive functions and performance speed [136,137], visuospatial skills [134,138] and sensory functions (i.e. smell, hearing, vibratory discrimination, and stereognosis) [139]. Another decline can be found in abilities to activate, represent maintain, focus and process information [140].

The interindividual heterogeneous picture of cognitive functioning is influenced by a variety of factors [141]. Factors that are associated with higher cognitive functioning and less decline are higher education [142], an active lifestyle (ie cognitive, social and physical) [143-145] and nutrition, diet [146,147]. Furthermore, vascular diseases, genetics and biological processes (i.e. inflammation, neurobiological changes) are affecting aging and cognitive decline [141]. Although cognitive decline can be found in elderly, this decline does not lead into an impairment in daily activities [135] using different strategies to compensate the decline [148].

2.7.3. Dementia due to AD - typical cognitive impairment

Dementia due to AD has from its clinical view a typical progress in cognitive impairment. Before a cognitive impairment is noticed olfactory sense loss can be found as an symptom of prodromal stage of dementia [149]. In early stages the episodic memory is usually affected [74,150]. Progressed dementia is characterized by prominent amnesia and greater memory disorders with rapid forgetting and loss of orientation, executive dysfunction and deficits in other cognitive domains as language and semantic knowledge, visuospatial skills and attention [74,131,151,152] and deficits in abstract reasoning [84].

NIA-AA criteria fit these studies and differ between a amnestic, deficit of episodic memory especially learning and recall, and a non-amnestic, deficits in language, visuospatial and executive functions, variation [40]. The cognitive impairment leads to an affection of the everyday life.

The episodic memory deficit is mainly owing to an unsuccessful consolidation or storage rather than an ineffective retrieval of new information [153]. Especially impaired recognition and free recall and a rapid forgetting of new information (anterograde amnesia) but also the deficit of retrieve prior known information (retrograde amnesia) are found in dementia patients [84]. The non-declarative memory is less affected of dementia due to AD and the function to acquire and retain motor and perceptual skills stays mostly intact [84].

Other parts of cognitive impairment are BPSD. They occur usually in patients with moderate to severe dementia [154,155]. BPSD occur in form of depressive affection and agitation, e.g. aggressive behavior, irritability, apathy, disturbed sleep-wake cycle and motoric restlessness [156].

2.8 Scientific problem und aim of the work

Because of the big overlap of AD typical changes and age-related changes we must ask the question “what is normal aging and what is already a pre-stage of AD”. The overlap is graphically presented in Figure 4 and 5. Previous reports show that there are differences in predictive values of diagnostics depending on age [26]. The neuropathological pathways are not fully understood yet. The overlap of changes caused by aging processes and dementia changes [19] poses an extra challenge in identifying the roots of pathological chain reactions that are leading to cognitive decline. To investigate why protein accumulations in the brain can exist without causing symptoms, research must take account of a multifactorial view on the patients including multimorbidity, medical history, social and psychological status, and lifestyle behavior.

To become a clearer view on the causes of diseases psychiatry needs to go from syndromic diagnosis to a more biological base. The ATN profile classification is a way to define the disease in a biological way and might lead to a better understanding of the cause. The data of the memory clinic of Cologne were examinate for different age groups, to see how these groups differ from each other. The ATN profiles might lead to a clearer differentiation between older and younger patients with dementia.

Further we wanted to investigate how pathological Aβ influences the cognition in the different age groups to get a better understanding of the relation between biological changes and symptoms.

A future aim in clinical treatment should be building a heterogeneous picture of cognitive decline in patients: going away from a one-pointed disease-orientated treatment to a

preventive conscious society. Only with this paradigm change the society will be able to handle the burden of an aging society.

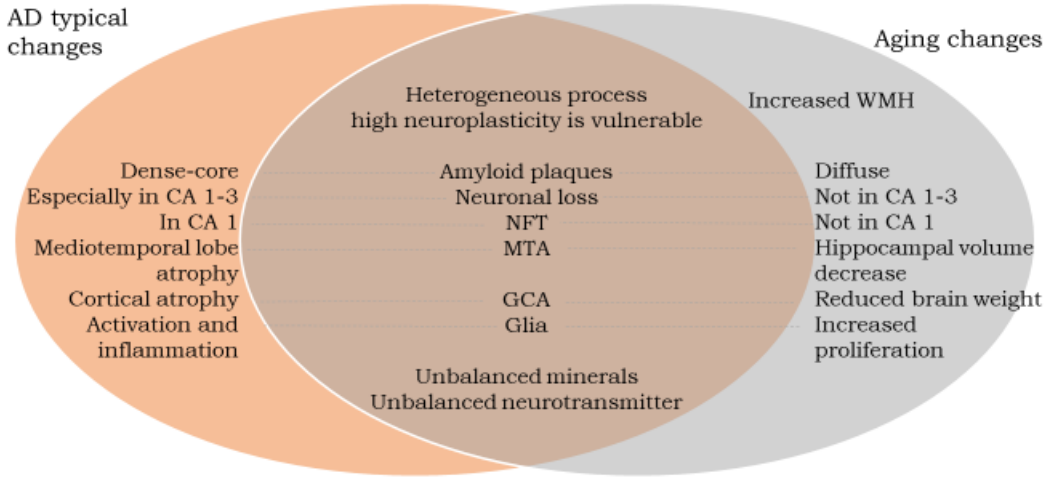

Figure 4: Comparison of pathological changes of AD and aging

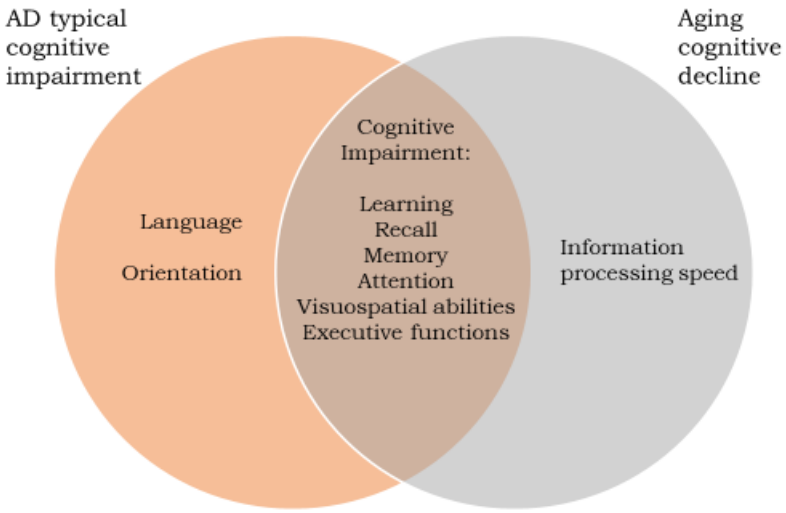

Figure 5: Comparison of cognitive decline between AD and aging

Legend:

CA = cornu ammonis regions in the hippocampus

NFT = neurofibrillary tangles

MTA = mediotemporal atrophy

WMH = white matter hyperintensities

GCA = global cortical atrophy

3. Material and methods

3.1 Methods

Standard protocol approvals. The study was approved by the local Ethics Committee (nr 20-1106).

3.1.1. Participants

This analysis was conducted based on datasets from patients at the interdisciplinary Center for Memory Disorders of the Department of Psychiatry of the University Hospital of Cologne, Germany seen between June 2015 and November 2019. The cohort included 750 patients. 269 with AD-typical and mixed dementia, 255 with MCI. The participants with dementia met dementia criteria defined by ICD-10. Inclusion criteria were the availability of an extended NPT, CSF biomarkers and the diagnosis of either MCI or dementia (AD, probable/possible AD or mixed dementia) (Figure 6). CSF sampling was performed as part of the diagnostic work-up and based on a shared decision-making process with the patients and their caregivers. All 222 participants with complete sets of CSF, NPT (MMSE, verbal fluency, categoric fluency, word list learning, word list recall, BNT, drawing figures, figures recall, TMT A, B, FCSRT), age and diagnosis: MCI, dementia caused by AD or mixed dementia have been chosen for this study (Figure 6). The participants were separated into two age groups: under 70 years older (70-) and 70 years or older (70+).

Exclusion criteria were known causes of cognitive impairment and other cognitive impairment forms, such as subjective cognitive impairment (SCI) (148), vascular dementia (1), posterior cortical atrophy (1), primary progressive aphasia (8), aphasia (2), Parkinson-dementia (12), Lewy-body-dementia (7), corticobasal degeneration (1), multiple system atrophy (1), frontotemporal dementia (7) and depression (38). Exclusion criteria also included a lack of information: no CSF, NPT, age or diagnosis (55).

Datasets were divided into two patients' age groups: age younger than 70 years ≙ 70- (n = 98) and 70 years and older ≙ 70+ (n = 124). The cut-off age of 70 years was chosen, due to the explorative nature of geriatric medicine based on previous reports [25,26].

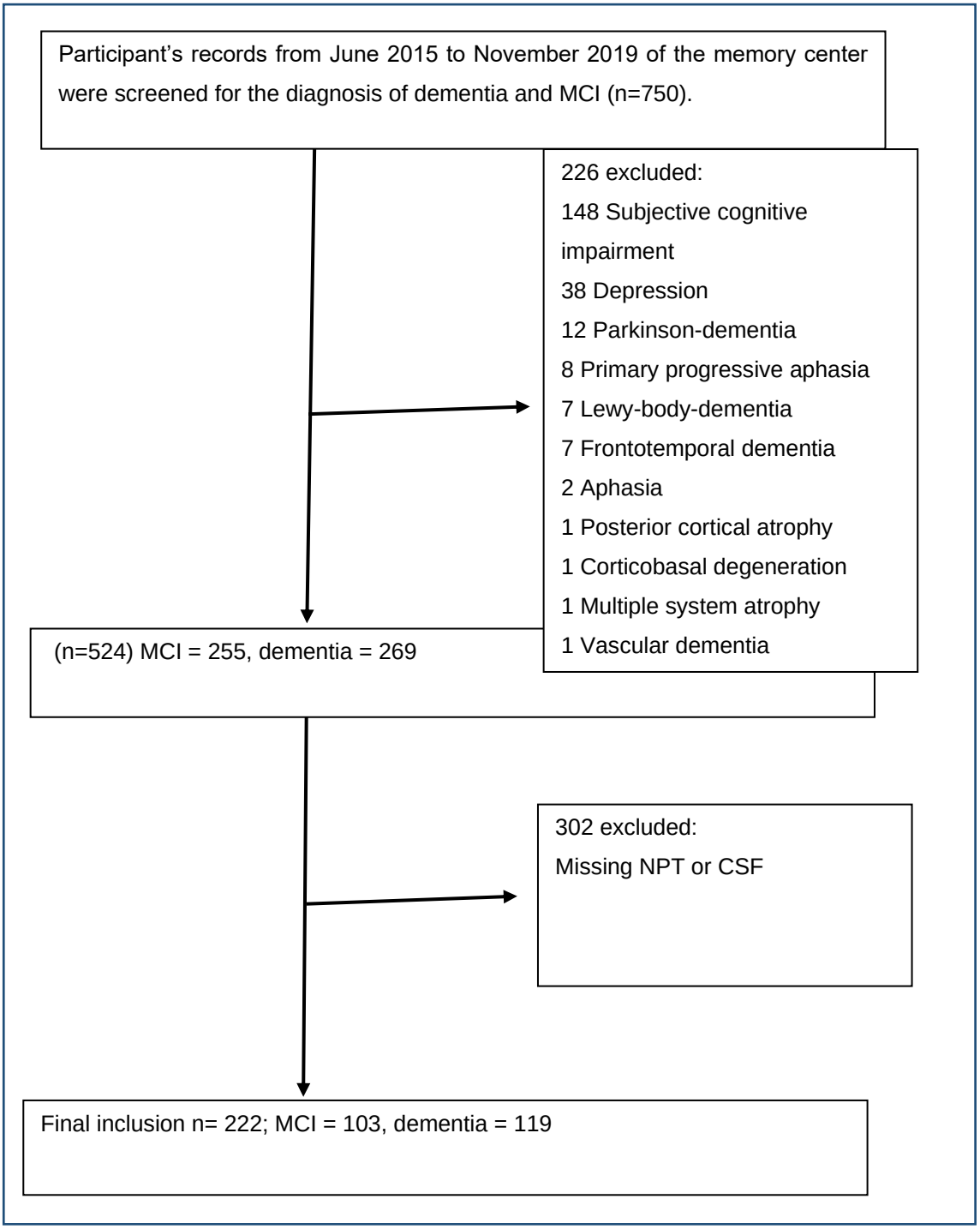

Figure 6: Flowchart inclusion criteria

3.1.2. Neuropsychological assessment

Cognitive performance was assessed with the Consortium to Establish a Registry for Alzheimer's Disease - Neuropsychology Plus test battery (CERAD-NP) [81,82]. The CERAD-NP includes verbal fluency, the BNT, MMSE [77], word list learning, recall and recognition, figures learning and recall, TMT A and b. Additionally, the FCSRT [157] and the geriatric depression scale (GDS) was performed. General cognitive impairment was assessed with MMSE (0-30

points), where higher scores reflect a higher cognitive performance. The memory score was calculated on the basis of the mean z-scores of the CERAD-NP tests, which are reflecting memory performance (i.e., figures recall, word list recall) as well as of the FCSRT free and total FCSRT recall values. Z-scores of the CERAD take age, gender and number of educational years into account [158]. As this is not the case for the FCSRT, its scores were standardized based upon data from all participants.

3.1.3. ATN profiles

The ATN classification system is based on the framework of the NIA-AA [20]. This utilizes the CSF and/or amyloid PET values $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio (Amyloid, A), CSF p-tau and/or tau PET values of neurofibrillary tangles (Tau, T) as well as neurodegeneration or neuronal injury as assessed by MRI, FDG PET or CSF t-tau (Neurodegeneration, N). The $A\beta_{42}/A\beta_{40}$ ratio is used to compensate individual differences in Aβ production and metabolism, reflecting pathological changes more accurately than $A\beta_{42}$ alone [159]. In this study ATN groups were classified by using only CSF data. As a possible option described in the NIA-AA framework and the most common diagnostic option in the participants.

According to this classification, presence of ATN biomarker changes is marked with a +, values within normal range with a -. For example, A-T-N- indicates normal biomarkers, while groups with A+ are defined in the new classification as belonging to an *Alzheimer's continuum*. An A+T+N± profile defines AD. A- accompanied by either pathologic T or N is categorized as non-AD pathologic category. In line with the NIA-AA framework groups were collapsed into non-AD profiles and AD-continuum profiles.

All data was collected in the Center for Memory Disorders at the University Hospital of Cologne from physicians specialized in cognitive disorders through a standard questionnaire. CSF was analyzed in the University clinical Center Cologne as followed:

A+: $A\beta_{42}$: < 600 pg/ml and/ or $A\beta_{42}/A\beta_{40}$: < 0,1

T+: p-tau > 61 pg/ ml

N+: t-tau >290 pg/ ml after 27.04.17 or > 466 pg/ ml before 27.04.17

3.1.4. Variables

The main endpoints were differences in ATN profiles between the two age groups (70- and 70+). And the influence of $A\beta_{42}$, p-tau und t-tau of the cognition between age groups depending on ATN profiles.

3.2 Statistics

For the statistical analysis, continuous variables are presented as mean ± standard deviation (SD) and median ± quartile, categorical variables as count and percentage. Differences between ATN profile distributions among the two age groups were examined with the exact Fisher and Chi-squared test [160]. The Chi-squared test was used as a statistical test method that can make statements about the relationship between variables that are scaled nominally. Differences of quantitative variables between the two age groups were examined with the Mann-Whitney U test [161]. The Mann-Whitney U test was used because the data was not normally distributed. The test investigates whether the middle ranks of two independent samples differ significantly.

Correlations were tested among age, MMSE, Memory, t-tau, p-tau, $A\beta_{42}$ and $A\beta_{42}/ A\beta_{40}$. Cognitive performance (MMSE, Memory score and NPT results) between amyloid categories was compared with Mann-Whitney U test in each age group because of the ordinal scale levels. Diagnosis distribution (nominal) between the age groups was tested with Chi-squared test. The influence of amyloid pathology and age on measures on MMSE and Memory was analyzed by multiple linear regression for each age group separated including the variables A, gender, age, GDS, t-tau, p-tau, $A\beta_{42}$ and $A\beta_{42}/ A\beta_{40}$. The regression analysis was used after correlations among some variables were found, a linear relation is assumed.

Statistical significance was set to a two-sided significance level of 0.05. Data analysis was performed with the SPSS version 26.0 (SPSS, Chicago, IL, USA). Statistical advice was provided by Ingrid Becker (Cologne Institute for Medical Statistics and Bioinformatics).

To analyze the population of the memory clinic Cologne the general demographics of the participants were shown. Datasets were divided in age-groups: on the one hand all participants under 70 years and on the other hand participants 70 years old or older. Furthermore, the ATN-scheme was applied to the participants and distribution and further demographics were shown. To compare ATN profiles between age-groups and neurocognition statistical methods were used as described above.

4.1 Memory clinic population

4.1.1. Memory clinic population

The memory clinic population contains 750 participants. After excluding subjects with other diagnosis than SCI / MCI / dementia probable caused by AD or mixed dementia the total number of participants reduces to 673. Age increased with syndrome severity (from 64.1 y in SCI to 68.3 y in MCI and 72.7 y in dementia). Gender distribution showed that there were 35 more females than males (85 females (F) to 62 males (M) in SCI, 122 F to 129 M in MCI and 142 F to 123 M in dementia). Participants with SCI had a higher education (14.5 y to 12.6 years in each MCI and 12.2 y dementia). In the analysis of the cerebral spinal fluid $A\beta_{42}$ decreased with syndrome severity (from 810 pg/ml in SCI to 653 pg/ml in MCI to 510 pg/ml in dementia). A same pathological increase is shown for p-tau (from 49 pg/ml in SCI to 71 pg /ml in MCI and 82 pg /ml in dementia) and t-tau (from 449 in SCI to 597 in MCI and 635 in dementia) (table 4). All cognitive test results decrease with syndrome severity as seen in table 4: Demographic data of the memory clinic.

Table 4: Demographic data of the memory clinic

		SCI		MCI		Dementia	
		Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)
Age		64.10	148	68.31	256	72.70	269
Gender	Female		85		122		142
	Male		62		129		123
Education in y		14.47		12.58		12.22	
MMSE		29.01		27.00		20.93	
Memory		-		-2.25		-6.28	
$A\beta_{42}$ [pg/ml]		792.75		677.93		506.45	
$A\beta_{42}$/ $A\beta_{40}$ ratio		0.11		0.09		0.07	
p-tau [pg/ml]		387.95		564.16		681.42	
t-tau [pg/ml]		56.90		65.92		82.53	

Abbreviations: $A\beta_{42}$, amyloid β1-42; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; n, number; p-tau, phosphorylated tau protein; SCI, subjective cognitive impairment; SD, standard deviation; t-tau, total tau protein; y, years

4.1.2. Demographics of the study population

Demographic characteristics of the sample are presented in table 5. The average age was 69.5 ±9.1 years in total, 61.1 ±6.3 years in the 70- and 76.2 ±4.0 years in the 70+ group. The 70+ group had more datasets (124) than the 70- group (98). Gender was equally distributed (110 F,112 M) but differed between 70+ and 70- groups with a lower number of women (42 F vs 56 M) in the 70- and a higher number of women (68F vs 56 M) in the 70+ group. The gender difference between age groups, however, did not reach statistical significance. In total, 103 patients were diagnosed with MCI and 120 with dementia (AD, possible / probable AD and mixed dementia). There were more MCI (55) and dementia (69) cases in the 70+ group than in the 70- group (48 MCI, 50 dementia cases, respectively) without statistically significant differences. The 70+ patients showed a significantly lower number of education years compared to the 70- group (p = 0.001; 70-: 13.3 ±2.9; 70+: 11.5 ±2.7). In the analysis of CSF, the $A\beta_{42}$/ $A\beta_{40}$ ratio was significantly lower in datasets of 70+ than 70- (p = 0.05; 70-: 0.10 ±0.08; 70+: 0.07 ±0.03). The difference was independent from the severity of the diagnosis

(70-: MCI: 0.10, dementia: 0.09; 70+: MCI: 0.08, dementia: 0.07). $A\beta_{42,}$ p-tau and t-tau values showed no significant difference among the age groups.

Table 5: Characteristics of the study population divided into age groups 70- and 70+ (n = 222)

		70-			70+			Mann-Whitney U
		Median (25.-75.)	Mean (SD)	n (%)	Median (25.-75.)	Mean (SD)	n (%)	p-value †
Age			61.1 (±6.3)	98		76.2 (±4.0)	124	
Gender	Female			42 (42.9)			68 (54.8)	
	Male			56 (57.1)			56 (45.2)	
Diagnosis	MCI			48 (49.0)			55 (44.4)	
	Dementia			50 (51.0)			69 (55.6)	
Education in years		12.5 (11.0-16.0)	13.3 (±2.9)		11.0 (10.0-13.0)	11.5 (±2.7)		0.001*
MMSE		25.0 (21.0-27.0)	23.8 (±4.8)		25.0 (21.0-27.0)	23.7 (±4.6)		0.785
$A\beta_{42}$ [pg/ml]		551.7 (394.1 - 721.3)	608.1 (±313.1)		527.9 (426.9 - 653.9)	567.7 (±231.3)		0.646
$A\beta_{42}$/ $A\beta_{40}$ ratio		0.07 (0.05 0.13)	-0.10 (±0.08)		0.06 (0.05 0.09)	-0.07 (±0.03)		0.050*
p-tau [pg/ml]		69.0 (46.0 -90.0)	73.0 (±37.5)		71.0 (53.0 - 94.0)	76.0 (±35.5)		0.335
t-tau [pg/ml]		541.5 (394.1 844.7)	-681.3 (±476.0)		559.1 (410.6 727.0)	-587.2 (±237.4)		0.875

Abbreviations: SD, standard deviation; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; $A\beta_{42}$, amyloid β1-42; p-tau, phosphorylated tau protein; t-tau, total tau protein; 70-, under 70 years old; 70+, over/ and 70 years old

*Significant at significant level alpha of .05.

† Mann-Whitney U

4.2 Correlations

To see if the variables are standing in any connection with each other, correlation analysis was used. Age correlated significantly with Aβ42/ Aβ40 ratio (p=0.011) and t-tau (p=0.046). Cognitive scores as MMSE and Memory Score showed significant correlations with Aβ42 (MMSE: p=0.017, Memory: p=0.001), Aβ42/ Aβ40 ratio (MMSE: p=0.045, Memory p=0.004), t-tau (MMSE: p=0.002, Memory: p=0.018) and p-tau (MMSE: p<0.001, Memory: p=0.001).

4.3 ATN scheme

4.3.1. ATN profiles

Participants were classified with the NIA-AA ATN scheme depending on the CSF biomarkers as described before. Full data is shown in table 6. 9.5% were identified as with normal biomarkers. The Alzheimer's continuum profiles (including all A+ profiles) constituted 77.6% of all patients. With 51,6% of the cases, A+T+N+ was the most common group among the datasets of all participants in our sample followed by A+T-N- (13.1%), A-T-N- (9,5%), A+T-N+ (8.6%), A-T-N+ (7.7%) and A+T+N- and A-T+N+ (both 4.5%). Least represented was A-T+N- with 0.9%.

The distribution of all ATN profiles was not significantly different between the two age groups using the Fisher exact test (p = 0.052). Non-Alzheimer's pathology groups were represented by less participants, especially in the older group (table 6).

Descriptively, among the two age groups there were more younger participants identified with normal biomarkers than the 70+ ones (12.2% 70- and 7.3% 70+). A+T+N+ was the most common group in each age group (49.0% for 70- and 53.6% for 70+). 70+ datasets had a higher rate of Alzheimer's continuum profiles than 70- ones (69.4% 70- and 84% 70+).

A significant difference was found over Alzheimer's continuum profiles vs non-Alzheimer's continuum profiles (p = 0.018) (Figure 7) between the two age groups, classifying 70+ datasets more often as Alzheimer's continuum than 70-. The classic AD A+T+N- without extra neurodegeneration is less represented in both age groups (2.0 % 70- and 6.5% 70+).

Table 6: ATN profiles

	n	Normal	Alzheimer's continuum				Non-Alzheimer's pathology		
	(%)		Alzheimer's pathological change	Alzheimer's Disease		Alzheimer's and concomitant suspected and non-Alzheimer's pathological change			
		A-T-N-	A+T-N-	A+T+N-	A+T+N+	A+T-N+	A-T+N-	A-T-N+	A-T+N+
70-	98 (100)	12 (12.2)	13 (13.3)	2 (2.0)	48 (49.0)	5 (5.1)	0 (0)	12 (12.2)	6 (6.1)
70+	124 (100)	9 (7.3)	16 (12.9)	8 (6.5)	66 (53.2)	14 (11.3)	2 (1.6)	5 (4.0)	4 (3.2)
total	222 (100)	21 (9.5)	29 (13.1)	10 (4.5)	115 (51.8)	19 (8.6)	2 (0.9)	17 (7.7)	10 (4.5)

Abbreviations: A, Amyloid; AD, Alzheimer's disease; N, Neurodegeneration; n, number; T, Tau protein; 70-, under 70 years old; 70+, over/ and 70 years old

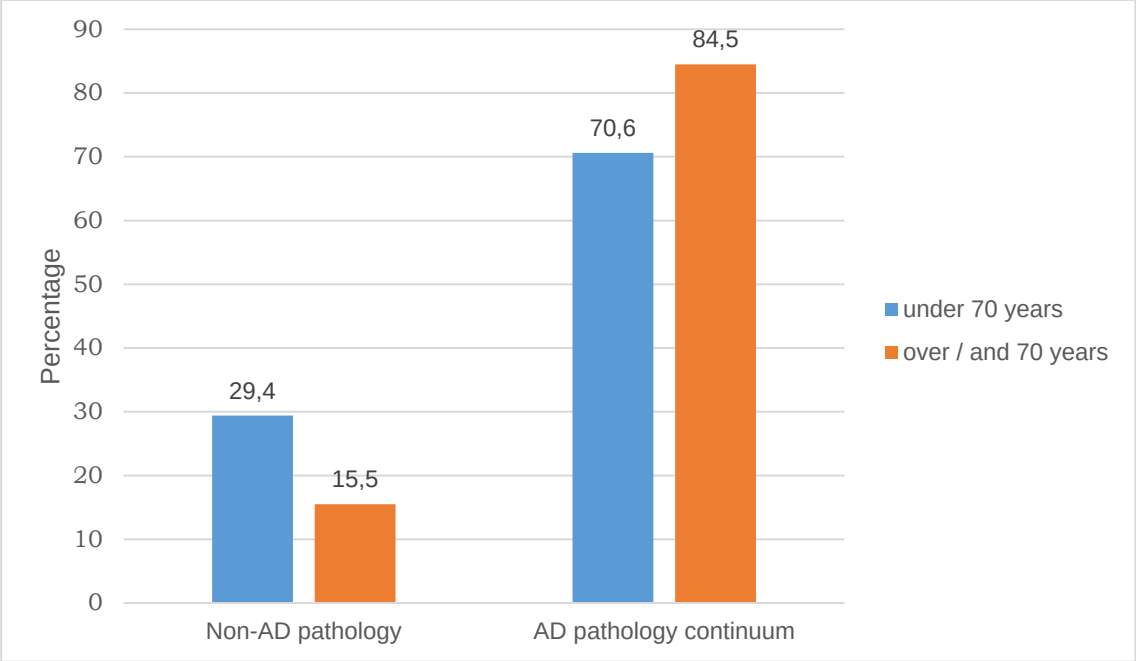

Figure 7: Distribution of non-AD vs Alzheimer's continuum in 70-/70+.

Abbreviations: AD, Alzheimer's disease; 70-, under 70 years old; 70+, over/ and 70 years old;
Non-Alzheimer's pathology profiles: A-T+N-, A-T-N+, A-T+N+
Alzheimer's continuum profiles: A+T-N-, A+T+N-, A+T+N+, A+T-N+

To see if the Alzheimer's continuum is a phenomenon of dementia and significant differences only based on distribution of diagnosis between the age groups, Chi-squared test was used ($p = 0.291$). No significant differences between diagnosis distribution between the two age groups were found (Figure 8 and Table 7).

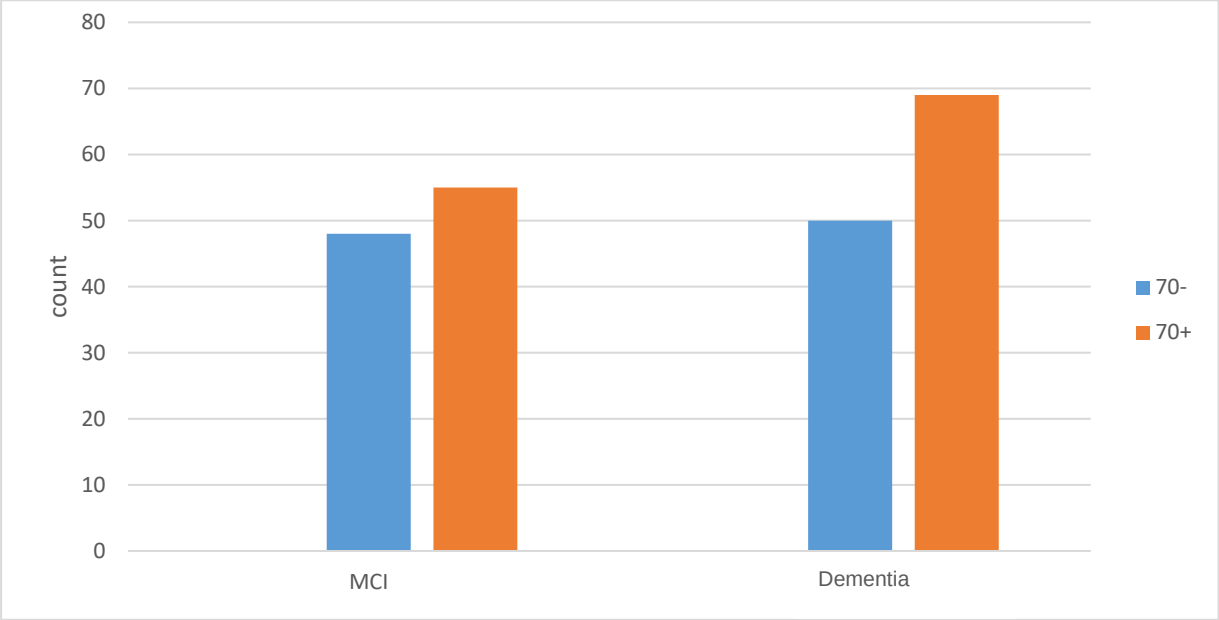

Figure 8: Distribution of diagnosis between age groups

Table 7: ATN profiles among diagnosis between age groups

	70-		*70+*	
	MCI n (%)	Dementia n (%)	MCI n (%)	Dementia n (%)
A-T-N-	11 (11.2)	5 (5.1)	8 (6.5)	2 (1.6)
A+T-N-	5 (5.1)	4 (4.1)	7 (5.6)	8 (6.5)
A+T+N-	0 (0.0)	2 (2.0)	3 (2.4)	4 (3.2)
A+T+N+	16 (16.3)	33 (33.7)	22 (17.7)	43 (34.7)
A+T-N+	2 (2.0)	3 (3.1)	6 (4.8)	8 (6.5)
A-T+N-	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)
A-T-N+	11 (11.2)	1 (1.0)	5 (4.0)	0 (0.0)
A-T+N+	3 (3.1)	2 (2.0)	2 (1.6)	4 (3.2)

Abbreviations: A, Amyloid; AD, Alzheimer's disease; MCI, mild cognitive impairment; N, Neurodegeneration; n, number; T, Tau protein; 70-, under 70 years old; 70+, over/ and 70 years old

4.3.2. Amyloid pathology and cognition

Figure 9 displays the MMSE score distribution among the amyloid state (A+ vs A-) according to age group. Both cognitive scores (MMSE and Memory) differed significantly between the A groups in the 70- group (MMSE $p < 0.001$, Memory $p < 0.001$) using the Mann-Whitney U test, whereas only the memory score was significantly associated with the amyloid state in the 70+ group (MMSE $p = 0.166$, Memory $p = 0.023$). The boxplot charts display the trend of slight deterioration of MMSE for 70- datasets with abnormal Aβ. However, a strong overlap can still be seen graphically.

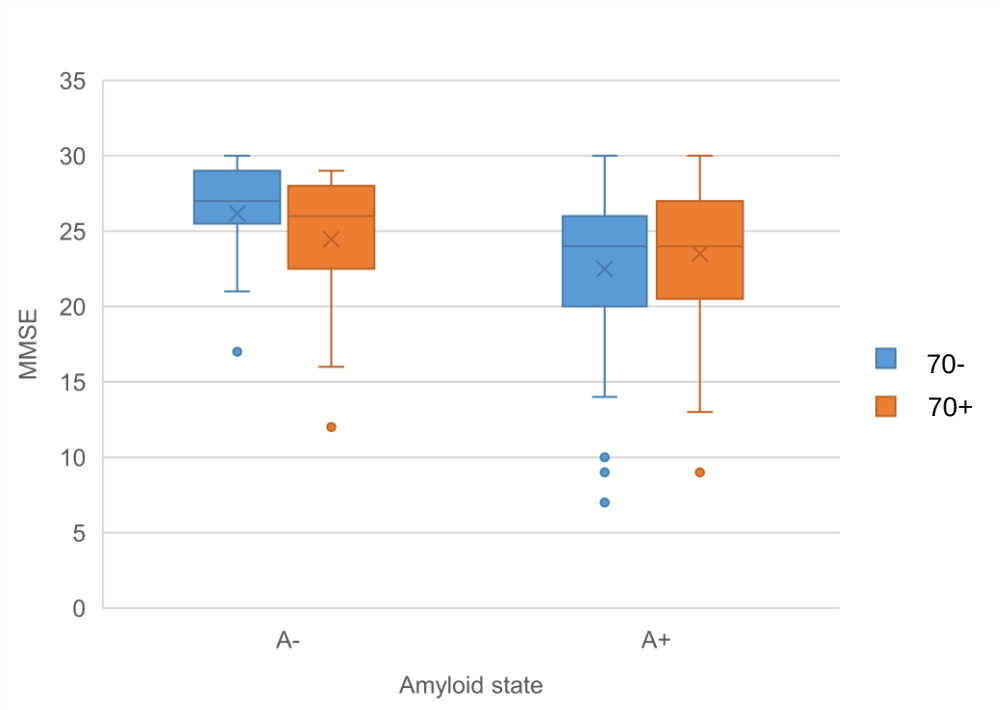

Figure 9: Performance on MMSE dependent on age and amyloid state

Other cognitive domains including language, verbal fluency and visuospatial function did not show any significant differences between A+/A- (table 8).

Table 8: Comparison of cognitive performance of groups with different amyloid pathology state for each age group

Test	70- p-values†	70+ p-values†
MMSE		
Total	<0.001*	0.166
z-score	0.001*	0.669
Memory score		
z-score	<0.001*	0.023*
BNT		
Total	0.173	0.625
z-score	0.181	0.638
Semantic fluency		
Total	0.584	0.234
z-score	0.642	0.254
Word list learning		
Total	<0.001*	0.008*
z-score	<0.001*	0.001*
Word list recall		
Total	<0.001*	0.158
z-score	<0.001*	0.040*
Figures drawing		
Total	0.024*	0.662
z-score	0.052	0.471
Figures recall		
Total	<0.001*	0.007*
z-score	<0.001*	0.010*
Phonematic fluency		
Total	0.587	0.288
z-score	0.762	0.379
TMT A	0.062	0.141
TMT B	0.009*	0.237
FSCRT		
free	0.020*	0.017*
cued	0.002*	0.169

Abbreviations: BNT, Boston-Naming Test; FCSRT, free and cued selective reminding test; MMSE, mini-mental state examination; Memory Score includes z-scores of figures recall, word list recall, FCSRT free and total; BNT, Boston-Naming Test; TMT, trail making test

*Significant at significant level alpha of .05.

† Mann-Whitney U test between A groups

4.4 Regression analysis

In order to statistically examine the correlation results further, regression analyses were carried out. Since we found a significant correlation between $A\beta_{42}/A\beta_{40}$ and age and between $A\beta_{42}/A\beta_{40,}$ p-tau and MMSE/ Memory, these were the main focus points of our regression analysis.

In the regression for MMSE (dependent variable) without dividing into age groups over $A\beta_{42}$, $A\beta_{42}/A\beta_{40}$, t-tau, p-tau, gender, GDS and age (independent variables), biomarkers showed significant results $A\beta_{42}$ ($p = 0.003$), $A\beta_{42}/A\beta_{40}$ ($p = 0.034$), p-tau ($p = 0.004$), GDS ($p = 0.028$). Age ($p = 0.174$), t-tau ($p = 0.989$) and gender ($p = 0.781$) had no significant result.
After dividing the datasets into the age groups, a multiple linear regression analysis with backwards elimination was rerun. In the 70- group the regression for MMSE over $A\beta_{42}/A\beta_{40}$, gender, GDS and age, showed a significant influence of $A\beta_{42}/A\beta_{40}$ ($p\ 0 = 0.004$) in the last model. In the 70+ group the last variable standing was GDS ($p = 0.006$).
The regression coefficient B of $A\beta_{42}/A\beta_{40}$ was different (70-: 30.883, 70+: 2.599), however, confidence intervals for B overlapped (70-: [-1.358 – 63.123]; 70+: [-30.24 – 35.442]), therefore, the statistical difference is not significant.

The same analysis was carried out excluding A- datasets but came to a similar result.
Another regression for MMSE over age, gender, GDS and p-tau showed a significant influence of p-tau in the 70- group ($p < 0.001$ [-0.068 - -0.014]) but no significant influence of p-tau in the 70+ group ($p = 0.070$ [-0.048 – 0.002], but for GDS in the 70+ group ($p = 0.011$ [-0.669 - -0.073] and not significant in the 70- group ($p = 0.259$ [-0.130 – 0.476]). Because of the overlapping confidence intervals, the different results are not significant between the two age groups.
The same result was found for regression analysis for MMSE over gender, age, GDS and Aβ42.

In the regression for Memory (dependent variable) without dividing into age groups over $A\beta_{42}$, $A\beta_{42}/A\beta_{40}$, t-tau, p-tau, gender, GDS and age (independent variables). Only p-tau showed a significant result (p = 0.011). Age had no significant influence (p = 0.923).

After dividing the datasets into the age groups, regression analysis was run again. In the 70- group the regression for Memory over $A\beta_{42}/A\beta_{40}$, p-tau, gender, GDS and age. No significant influence of any specific variable or difference between the age groups was found. After backwards elimination $A\beta_{42}/A\beta_{40}$ showed a significant result (p= 0.01)
In the 70+ group no significant result was found.
The regression coefficient B for $A\beta_{42}/A\beta_{40}$ was different (70-: 8.449, 70+: 4.683), confidence intervals for B overlapped (70-: [-3.378 – 20.277]; 70+: [-4.851 – 14.216]), so that therefore, the statistical difference is not significant.
The same analysis was carried out excluding A- datasets but came to a similar result. A overview of the regression analyses is presented in table 9 and 10.

Table 9: Multiple linear Regression for the 70- group. Dependent variable MMSE, independent variables $A\beta_{42}/A\beta_{40}$, gender, GDS and age. After backwards elimination $A\beta_{42}/A\beta_{40}$ showed a significant result.

Dependent variable: MMSE						
	Variable (Backwards)	default	robust	Std.-error	Sig.	Confidence interval
70-	Constant	16.87 (20.60)		7.19 (1.30)	0.02* (<0.001*)	[2.49 – 31.26]
	$A\beta_{42}/A\beta_{40}$	30.88 (41.32)	0.26 0.35	16.12 (14.0)	0.06 (0.004*)	[-1.36 – 63.12] ([13.35 – 69.29])
	Gender	1.40	0.15	1.24	0.26	[-1.07 – 3.87]
	GDS	0.16	0.12	0.18	0.38	[-0.20 – 0.52]
	Age	0.03	0.03	0.10	0.79	[-0.18 – 0.24]
	R^2	0.146				
	Adjusted R^2	0.090				
	F-statistic	0.044* (0.004*)				

Abbreviations: $A\beta_{42}$ /$A\beta_{40}$, amyloid β1-42/40 ratio; GDS, geriatric depression scale; Sig, Significance; Std, Standard

*Significant at significant level alpha of .05.

Table 10: Multiple linear regression for the 70+ group. Dependent variable: MMSE, independent variables: A ratio, gender, GDS and age. After backwards elimination GDS showed a significant result

Dependent variable: MMSE						
	Variable (Backwards)	default	robust	Std.-error	Sig.	Confidence interval
70+	Constant	34.07		9.28	<0.001*	
		(25.32)		(0.66)	(0.003*)	
	$A\beta_{42}/A\beta_{40}$	2.60	0.02	16.54	0.88	[-30.24 – 35.44]
	Gender	-0.42	-0.04	0.95	0.66	[-2.30 – 1.47]
	GDS	-0.46	-0.29	0.16	0.006*	[-0.79 – -0.13]
		(-0.47)	(-0.29)	(0.15)	(0.003*)	[-0.77 - -0.16]
	Age	-0.11	-0.09	0.12	0.35	[-0.34 – 0.12]
	R^2	0.096				
	Adjusted R^2	0.058				
	F-statistic	0.047*				
		(0.003*)				

Abbreviations: $A\beta_{42}$ /$A\beta_{40}$, amyloid β1-42/40 ratio; GDS, geriatric depression scale; Sig, Significance; Std, Standard

*Significant at significant level alpha of .05.

5. Discussion

In the present study the goal was to show differences and similarities between the older and younger patients of a memory clinic, to investigate the neuropathologies with the ATN scheme and to compare the influence of amyloid to their cognition.

The cut-off age of 70 years was chosen in an explorative way. Older studies already show that the predictive values of biomarkers decrease in older age [26]. Our results support the hypothesis that differences in biomarkers are depending on age. The nuances of changes in pathology, and therefore neuropathological classification, should be further studied and might need cut off values depending on age. Studies with large populations could choose a smaller classification (e.g., 4 groups: 60y/70y/80y/90y) and thus also determine age-adaptive values for biomarkers.

Both cognitive scores (MMSE and Memory) differed significantly between the A+/- groups in the 70- group, whereas only the memory score was significantly associated with the amyloid state in the 70+ group. Showing that the memory score is more sensitive to amyloid effects than the MMSE. This implicates that especially in advanced age a detailed, specialized neuropsychological assessment is needed to become first hints to the biological cause of the cognitive impairment. These findings are in agreement with the specific cognitive decline in AD typical dementia [74,150].

In light of the frequent presence of amyloid in the brains of cognitively healthy older persons, similar to the amyloid deposition observed in AD, and of the loss of Aβ protective function after aggregation [162], core features of aging should be taken into account for AD identification in advanced age. A biological definition and therefore, different therapy options, comes with opportunities, but also challenges in the older patients. Furthermore, a comprehensive geriatric assessment might be helpful especially in elderly patients to disclose further factors – physical, social, nutritional, therapeutic – and geriatric syndromes exerting a strong influence on cognitive performance.

As expected, age correlated significantly with $A\beta_{42}$/ $A\beta_{40}$ ratio and t-tau. Since amyloid is a pathology of older age and can be found in cognitive normal adults [91], interpretation of CSF biomarkers need to take consideration age as an important factor for positive amyloid and further age-related cognitive pathologies [87]. Age can be either a risk factor for amyloid pathology and dementia or must also be seen as an independent heterogeneous process.

Future studies are needed to find age-matched cut-off values for CSF biomarkers as they are already used in neuropsychology [163].

Cognitive scores as MMSE and Memory Score showed significant correlations with biomarkers $A\beta_{42}$, $A\beta_{42}$/ $A\beta_{40}$ ratio, t-tau and p-tau, which support the amyloid cascade hypothesis and the general connection between the neuropathology and the symptoms. Though further investigation is needed to completely understand the pathological pathway. And the new biologica therapy will show if a reduction of amyloid in an early state will prevent patients from a severe disease progression.

After dividing the datasets into the age groups, a multiple linear regression analysis with backwards elimination was run. In the 70- group the regression for MMSE over $A\beta_{42}/A\beta_{40}$, gender, GDS and age, showed in the last model a significant influence of $A\beta_{42}/A\beta_{40}$ (p 0 = 0.004). In the 70+ group the last variable standing was GDS (p = 0.006).
The regression coefficient B of $A\beta_{42}/A\beta_{40}$ was different (70-: 30.883, 70+: 2.599), however, confidence intervals for B overlapped (70-: [-1.358 – 63.123]; 70+: [-30.24 – 35.442]), so that therefore, the statistical difference is not significant, and interpretations must be made with caution. The results first assume a weaker influence of $A\beta_{42}/A\beta_{40}$ in older patients without confirming it statistically.
We chose the multiple linear regression assuming a linear relation between the variables. Other statistical analysis might be a better fit.

After all, these results support the wider view of interpretation of biomarkers in older patients [19,26]. Despite a similar ATN expression and an even higher A + rate in older patients due to the overlap between AD and aging [19,164], the amyloid pathology seems to strongly contribute to an increased cognitive impairment only in the younger ones. The amyloid pathology of the elder patients might be a prodromal stage of dementia [91], in which a cognitive decline has already happened due to other, eventually age-related diseases, normal aging or any mixed state of these three, showing the multifaced variations of late life cognitive impairment and age-related pathologies [12,165]. Thus, amyloid pathologies contribute in various still not totally understood ways to pathological changes [166] and need further research.

An interesting finding of the present analysis is that younger participants' datasets but not those from 70+ patients showed a significant correlation between general cognitive decline as assessed by MMSE and amyloid pathology. The absence of a correlation between severity of cognitive impairment and Aβ burden level in the 70+ group is in alignment with previous amyloid imaging reports confirming that amyloid deposition starts many years before significant cognitive symptoms occur, and that the Aβ burden in the brain remains approximately the same throughout the disease [167].

This interpretation might be further revised in the presence of information regarding domains of patients beyond the neuropsychiatric one. For older patients a comprehensive geriatric assessment might narrow the currently wide overlap in cognitive scores in relation to biomarker distribution.

The present analysis showed that the majority of datasets could be classified as A+T+N+ and that 70+ patients belonged significantly more often to the Alzheimer's continuum ATN profile than younger patients without having a significant higher rate of dementia diagnosis. This could be interpretated by the neuropathological changes that come with a higher age or could be seen as the higher incidence of Alzheimer disease in old age.
Differences of distribution over all ATN groups are non-significant (p=0.188), but probably due to our sample size and the difficult statistical interpretation of small subgroups. If reduced to A+ vs A- groups older and younger patients show a significant different distribution (p=0.038), with a bigger part of A+ in the older group. To cut out the limited power of the current study, a very large sample size will be needed in future studies to assess this framework and show significant results.

However, as much as almost half of the datasets did belong to the A+T+N+ group and therefore show not only Alzheimer typical changes but further other neurodegenerations. In agreement with recent studies this showed that although AD is still the strongest single driver of dementia, other age-related factors and a multifactorial cause with multiple pathological factors must be considered [12-14,168-170]. Indeed, conditions predisposing to dementia in advanced age beyond physiological alterations due to brain ageing [171,172] include sensory impairment, polypharmacy and iatrogenic reactions among others [173].

The fact, that an A+ result cannot differ between a prodromal stage of AD or AD, underlines the need of a wider perspective of the patients [87,89]. Recent studies show that AD is the biggest driver for dementia but less often as a single pathology than in a mixed pathology [12,14]. The abnormal amyloid protein deposits define AD as a biological construct. An even more accurate biological characterization of the underlying pathologies might lead to a better understanding of the sequence of steps that cause the cognitive impairment, which is associated with AD, and the multifactorial etiology of dementia [20].

To improve the use of the ATN classification and its interpretation across age ranges thereby reducing overlapping results, further studies are needed which prospectively use both the ATN system, a detailed neuropsychological assessment (e.g., CERAD) and, especially in advanced age, a systematic, multidimensional clinical evaluation (e.g., multidimensional prognostic

index). In particular, new biomarkers are required for other domains to complete a multidimensional view [20]. New plasma biomarkers (Aβ and p-tau) might become an easier way to access biological information. But because of the overlap of age-related changes and AD changes new additionally ways should not be forgotten and maybe new perspectives for example the positive sides of forgetting and their biological functionality might lead to a better understanding of dementia and finally complete the classification.

The higher percentage of A+ datasets in our study might be part of the selection bias of a memory clinic and can be found in another memory clinic for dementia cases probable caused by AD considering the inclusion of MCI and almost only dementia caused possible and probable by AD patients in our study [174].
Our results lead to the conclusion, that the ATN scheme is a good system to classify neuropathological changes, but might be clinically of more value for younger patients supporting the clarity of the cause of the cognitive impairment and opening up new treatment options, while for older patients an additionally more individual view with increased intention to age-related pathological changes [19] and diseases, social and psychological background and side effects of treatments would be useful.
In conclusion, although studies of ATN profiles among cognitively normal or mildly impaired individuals have been published [175-177], the results of the present analysis show, in agreement with previous reports, that aged adults differ from younger ones as far as biomarker-based diagnostic patterns of cognitive impairment are concerned.

All cognitive test results decreased with syndrome severity. As expected, education years are higher in syndromes with less severity. These results fit the diagnosis criteria of cognitive impairment and education can be interpretated as a protective factor in cognitive impairment. Education is also a suggested factor for the decrease in the incidence of dementia [33,147].

In the selecting of our datasets, the younger group is relatively young for dementia patients (61y), which could have influence on the statistical results. Another selection bias is that our study represents mostly white race, has no patients from nursing or retirement homes and gender representation differs in the two age groups, thus, the conclusions may not be generalized to a larger population. In the analysis of CSF in the study population showed that Aβ42/ Aβ40 ratio was significantly lower in datasets of 70+ than 70-, suggesting a higher level of brain amyloid deposition in older patients. These results were independent of the diagnosis and support a differentiated view between age groups.

Further, this study has several limitations. Beside the cross-sectional nature of the analysis and a selection bias related to CSF measurements as well as to mainly health-conscious, educated patients, also the relatively low sample size in some subgroups of the ATN profiles due to the large number of profiles and the rarity of some of them, which reduced the generalizability of the results and warrant further longitudinal research on larger patient groups. The statistically power of the results is limited due to the wide overlap of value range and must be interpreted carefully.
Furthermore, only CSF biomarkers were used to categorize the ATN groups, although other or combined diagnostical methods (ie. PET and MRI) show higher accuracy [178,179].

The strength of this study is the comparison between younger and older patients for ATN and cognition and a literature comparison between AD and aging, since this is not as present in medical research as it is important for clinical work. Also, the use of memory clinic patients supports the clinical use of this data instead for just research purposes.
To achieve a successful treatment prevention, medical- and non-medical treatments and social interventions should be closely intertwined [73,180] and patient should be seen in a multifactorial view with epigenetic, genetic, medical and social impediments.

All in all, aging and AD need to be more understood (ie. aging processes, active forgetting and the amyloid pathway [56,181]) and prevention needs to move to the front of the medical understanding of society in order to master future challenges. Although immunotherapy against amyloid might be an option in the future, just a small number of patients will be able to get the treatment. Other treatment options and strategies should not be affected by a partial solution. Findings of amyloid, especially in advanced age, should not limit further investigations of causes for dementia as mixed pathologies can often be found. Amyloid pathology increases with age, age-related cut-off values might clarify the pathology and set the right emphasis on the diagnostic findings. The ATN classification might help to neuropathologically categorize patients with syndromic dementia, going from a symptom-based diagnostic to a biological based diagnostic. A specialized neuropsychological testing appears also in advanced age to be key in studies investigating the role of amyloid pathology in cognitive decline. Other factors that should be systematically taken into account, however, include solid information about vascular risk factors and vascular comorbidities [103], multiple neuropathologies and multidimensional geriatric syndromes.

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7. Attachment

7.1 List of figures

7.2 List of tables