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Neuropsychiatric symptoms in early stages of Alzheimer's disease

Associations with neuropathological changes and cognitive deficits

MAURITS JOHANSSON | LUND UNIVERSITY





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Neuropsychiatric symptoms in early stages of Alzheimer's disease

Associations with neuropathological changes and cognitive deficits

Maurits Johansson



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<p>Abstract</p> <p>Alzheimer's disease (AD), the most common cause of dementia, is regarded as an illness of lost memories. Yet, its symptoms go beyond cognitive deficits. At some point, most persons with AD also develop neuropsychiatric symptoms (NPS), defined as disorders in emotions, motivation, or behavior. Previously thought to turn critical late in the disease, these manifestations are now shown related to adverse outcomes already in its early stages. However, their underlying neurobiological signature and their interplay with cognitive deficits have been understudied, hampering clinical management and the development of interventions.</p> <p>The aim of the thesis was to explore the relationship between NPS (especially apathy, anxiety, and depression), cognitive deficits, and core AD-related pathologies (amyloid-beta [Aβ], tau, and neurodegeneration) in non-demented individuals. The thesis further aimed to bring out a psychometrically evaluated rating scale for apathy in Swedish. Data were derived from the prospective and longitudinal Swedish BIOFINDER Study.</p> <p>In <i>paper I</i>, a Swedish version of the Apathy Evaluation Scale (AES) was demonstrated to perform similarly to the original English version and exhibited acceptable psychometric properties among cognitively unimpaired (CU) elderly and patients with mild cognitive impairment (MCI) or parkinsonian symptoms. In <i>paper II</i>, using a mixed sample of CU and MCI, apathy and anxiety were found associated with brain Aβ deposition as well as cognitive decline. A high level of anxiety further interacted with Aβ to predict even faster cognitive change. Moreover, apathy levels were found associated with frontotemporal atrophy. In <i>paper III</i>, studying CU with biomarker verified preclinical AD, the overall burden of Mild Behavioral Impairment (MBI), but not memory performance, was found associated with early brain tau pathology. In <i>paper IV</i>, examining CU elderly, levels of Aβ at study start were shown to be associated with a change in apathy or anxiety levels over time. A more rapid cognitive decline was also related to future higher levels of apathy. Yet, the effect by Aβ on future apathy was only partly mediated by cognitive change.</p> <p>Taken together, the thesis provides initial support for the Swedish version of the AES to be used in clinical and research settings. We further show that anxiety and apathy seem to be early clinical manifestations of underlying AD pathology, partly independent from cognitive impairment, and with the potential to predict subsequent cognitive decline.</p>		
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Associations with neuropathological changes and cognitive deficits

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MADE IN SWEDEN 

To Hanna

Bridging the gap between a mindless neurology and a brainless psychiatry

- Per Johansson, Ängelholm, 2010

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Abstract

Alzheimer's disease (AD), the most common cause of dementia, is regarded as an illness of lost memories. Yet, its symptoms go beyond cognitive deficits. At some point, most persons with AD also develop neuropsychiatric symptoms (NPS), defined as disorders in emotions, motivation, or behavior. Previously thought to turn critical late in the disease, these manifestations are now shown related to adverse outcomes already in its early stages. However, their underlying neurobiological signature and their interplay with cognitive deficits have been understudied, hampering clinical management and the development of interventions.

The aim of the thesis was to explore the relationship between NPS (especially apathy, anxiety, and depression), cognitive deficits, and core AD-related pathologies (amyloid-beta [$A\beta$], tau, and neurodegeneration) in non-demented individuals. The thesis further aimed to bring out a psychometrically evaluated rating scale for apathy in Swedish. Data were derived from the prospective and longitudinal Swedish BIOFINDER Study.

In *paper I*, a Swedish version of the Apathy Evaluation Scale (AES) was demonstrated to perform similarly to the original English version and exhibited acceptable psychometric properties among cognitively unimpaired (CU) elderly and patients with mild cognitive impairment (MCI) or parkinsonian symptoms. In *paper II*, using a mixed sample of CU and MCI, apathy and anxiety were found associated with brain $A\beta$ deposition as well as cognitive decline. A high level of anxiety further interacted with $A\beta$ to predict even faster cognitive change. Moreover, apathy levels were found associated with frontotemporal atrophy. In *paper III*, studying CU with biomarker verified preclinical AD, the overall burden of Mild Behavioral Impairment (MBI), but not memory performance, was found associated with early brain tau pathology. In *paper IV*, examining CU elderly, levels of $A\beta$ at study start were shown to be associated with a change in apathy or anxiety levels over time. A more rapid cognitive decline was also related to future higher levels of apathy. Yet, the effect by $A\beta$ on future apathy was only partly mediated by cognitive change.

Taken together, the thesis provides initial support for the Swedish version of the AES to be used in clinical and research settings. We further show that anxiety and apathy seem to be early clinical manifestations of underlying AD pathology, partly independent from cognitive impairment, and with the potential to predict subsequent cognitive decline.

Sammanfattning på svenska (Swedish summary)

Alzheimers sjukdom är den vanligaste degenerativa hjärnsjukdomen och starkt förknippad med fortlöpande försämring av den drabbades minne och andra tankeförmågor (kognitiva funktioner). Andra betydelsefulla och vanliga, men ofta förbisedda, yttringar av sjukdomen är påverkan av känsloliv, drivkraft och beteende. Sådana neuropsykiatriska symtom inkluderar depression, apati och ångest med ofta stort lidande för såväl den drabbade som närstående.

Vid Alzheimers sjukdom aggregerar och inlagras vissa proteiner såsom beta-amyloid (A β) och tau i hjärnan, med efterföljande nervcellsdöd (neurodegeneration). Inlagringen av A β börjar flera decennier innan symtom framträder. Kopplingen mellan dessa vävnadsförändringar och de kognitiva funktionsnedsättningarna har studerats flitigt, medan däremot de biologiska mekanismerna bakom uppkomst av neuropsykiatriska symtom inte är tillnärmelsevis så väl kartlagda. Framför allt saknas studier under tidiga sjukdomsstadier.

Denna avhandling avsåg att, under tidiga faser av Alzheimers sjukdom, utforska relationen mellan neuropsykiatriska symtom, underliggande sjukdomsförändringar och kognitiva funktionsnedsättningar. Vidare var målsättningen att ta fram en svensk version av ett internationellt etablerat apatiskattningsinstrument, för att på så vis kunna mäta och utvärdera apati. De studiedeltagare som undersökts ingår i de olika kohorterna i den longitudinella observationsstudien ”The Swedish BIOFINDER Study” (www.biofinder.se).

I en första studie, utförd på kognitivt friska äldre, patienter med lindrig kognitiv störning och patienter med parkinsonism, visades den svenska versionen av Apathy Evaluation Scale (AES) uppträda på ett likartat sätt som det engelska originalet samt ha goda mätmetodologiska egenskaper.

I en andra studie på individer utan demens, inkluderande kognitivt friska äldre och patienter med lindrig kognitiv störning, visades en ökad förekomst av A β i hjärnan vara kopplad till en högre grad av apati och ångest, men inte till depressiva symtom. En hög grad av apati respektive ångest kunde vidare förutsäga kognitiv försämring över tid. En accelererad försämring i kognition sågs hos dem med både hög

förekomst av A β och hög ångestnivå. Apati var ytterligare relaterat till vävnadsförlust i hjärnans tinninglob samt i mindre delar av pannloben.

I en tredje studie på kognitivt friska äldre, med samtidig patologisk förekomst av A β i hjärnan (preklinisk Alzheimers sjukdom), visades graden av neuropsykiatriska symtom, men inte minnesbesvär, vara relaterad till ökad förekomst av tau i de delar av hjärnan som drabbas tidigt vid Alzheimers sjukdom. Detta fynd talar för att neuropsykiatriska symtom är kopplade till Alzheimerpatologi tidigt i sjukdomsförloppet samt oberoende av den kognitiva nedsättningen.

I en fjärde studie visades A β , hos kognitivt friska äldre vara relaterat till utveckling av både apati och ångest över tid. Även en mer accelererad kognitiv svikt var kopplad till framtida ökad grad av apati. Effekten av A β på utveckling av apati visades däremot enbart i begränsad omfattning verka via den kognitiva försämringen. Detta antyder att A β kan ha en mer direkt inverkan på apatiutveckling.

Sammanfattningsvis talar våra studier för att den svenska versionen av AES kan tas i bruk i såväl en klinisk som vetenskaplig kontext. Vidare att de neuropsykiatriska symtomen apati och ångest utgör viktiga och tidiga kliniska manifestationer relaterade till underliggande Alzheimerpatologi (inklusive A β , tau och neurodegeneration), delvis oberoende av de kognitiva symtomen, men med potential att kunna förutsäga sådana över tid.

Abbreviations and acronyms

A β	Amyloid-beta
AD	Alzheimer's disease
ADAS-DR	The Alzheimer's Disease Assessment Scale – Cognitive Subscale - Delayed Memory Recall
AES	Apathy Evaluation Scale
APP	Amyloid precursor protein
AQT-CF	A Quick Test – the color form task
ARWMC	The Age-Related White Matter Change Scale
BF-I	The Swedish BIOFINDER Study I
BF-II	The Swedish BIOFINDER Study II
BPSD	Behavioral and Psychological Symptoms of Dementia
bvFTD	Behavioral variant of frontotemporal dementia
CBD	Corticobasal degeneration
CTT	Classical Test Theory
CSF	Cerebrospinal fluid
CU	Cognitively unimpaired
FDR	False Discovery Rate
FLAIR	Fluid-attenuated inversion recovery
FTLD	Frontotemporal lobe degeneration
GDS	Geriatric Depression Scale
HADS-A	The Hospital Anxiety and Depression Scale – Anxiety
HADS-D	The Hospital Anxiety and Depression Scale - Depression
ICD-10	The tenth revision of the International Classification of Diseases
LATE	Limbic-predominant age-related TDP-43 encephalopathy

LLD	Late-life depression
MBI	Mild Behavioral Impairment
MBI-C	Mild Behavioral Impairment – Checklist
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
mPACC5	modified Preclinical Alzheimer Cognitive Composite
MRI	Magnetic resonance imaging
ND	Neurodegenerative diseases
NfL	Neurofilament light chain
NFTs	Neurofibrillary tangles
NPS	Neuropsychiatric symptoms
PART	Primary Age-Related Tauopathy
PCA	Principal Component Analysis
PD	Parkinson’s disease
PDD	Parkinson’s disease dementia
PSP	Progressive supranuclear palsy
P-tau	Phosphorylated tau
DLB	Dementia with Lewy Bodies
PET	Positron emission tomography
ROI	Region of interest
SEm	Standard Error of Measurement
SSRI	Selective Serotonin Reuptake Inhibitor
TDP-43	TAR DNA-binding protein 43
VaD	Vascular Dementia
WML	White matter lesions

List of original publications

This thesis is based on the following original papers, referred to in the text by their Roman numerals:

- I. **Johansson, M.**, Johansson, P., Stomrud, E., Hagell, P., Hansson, O. Psychometric testing of a Swedish version of the Apathy Evaluation Scale. *Nordic Journal of Psychiatry* 2017; 71(6), 477-484.
- II. **Johansson, M.**, Stomrud, E., Lindberg, O., Westman, E., Johansson, P. M., van Westen, D., Mattsson, N., Hansson, O. Apathy and anxiety are early markers of Alzheimer's disease. *Neurobiology of Aging* 2020; 85, 74-82.
- III. **Johansson, M.**, Stomrud, E., Insel, P. S., Leuzy, A., Johansson, P. M., Smith, R., Ismail, Z., Janelidze, S., Palmqvist, S., van Westen, D., Mattsson-Carlgen, N., Hansson, O. Mild behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. *Translational Psychiatry* 2021; 11(1), 76.
- IV. **Johansson, M.**, Stomrud, E., Johansson, P. M., Svenningsson, A., Palmqvist, S., Janelidze, S., van Westen, D., Mattsson-Carlgen, N., Hansson, O. Development of apathy, anxiety, and depression in cognitively unimpaired older adults: effects of Alzheimer's disease pathology and cognitive decline. *Biological Psychiatry* 2022, Epub ahead of print Jan 28. doi: <https://doi.org/10.1016/j.biopsych.2022.01.012>.

Introduction

The thesis rationale in brief

The human mental abilities arise from neuronal activity and can be divided into the three categories cognition (thoughts), emotion (feelings), and drive (motivation and endurance)^{1,2}.

In degenerative brain diseases such as Alzheimer's disease (AD) neurons progressively lose function and ultimately succumb. In time, many of these neurodegenerative diseases (ND), display a profound impact on several areas of the brain³. Accordingly, all three overarching mental processes are likely to be affected during the disease progression^{4,6}.

In AD, cognitive deficits have been extensively studied and recognized, but less attention has been given to neuropsychiatric symptoms (NPS, disturbances in emotions, drive, or behavior), especially so during the early stages of disease⁷.

Even if advances have been made, the temporal and causal relationships between typical AD pathological changes, cognitive deficits, and disturbances in emotional or motivational processes are yet to be determined. A better understanding of the associations between these variables, together with psychometrically favorable assessments of NPS, might prove helpful in clinical settings, develop into new prognostic markers, and facilitate future intervention trials⁸.

Terminology of neuropsychiatric symptoms

As knowledge regarding neuropsychiatric symptoms in the field of ND has been acquired, disregarded, and eventually reconsidered, the terminology has evolved.

Neuropsychiatric symptoms (NPS) is an umbrella term encompassing a heterogeneous array of disturbances in emotion, motivation, and behavior, as well as psychotic symptoms in all stages of ND. The term covers disturbances such as depression, apathy, anxiety, aggressivity, agitation, irritability, disinhibition, euphoria, delusions, hallucinations, sleep disturbances, eating disorders, and aberrant motor behavior.

Behavioral and Psychological Symptoms of Dementia (BPSD) covers similar disturbances as NPS, yet these are restricted to more advanced stages of disease, when dementia has already developed⁹.

Mild Behavioral Impairment (MBI) is a recently developed construct that recognizes changes in behavior (here also including emotions and motivation) or personality late in life in individuals without dementia. MBI can be diagnosed prior to, in concert with, or somewhat after development of *Mild Cognitive Impairment* (MCI)¹⁰.

The Behavioral variant of Alzheimer's disease (bvAD) is considered a less common clinical presentation of AD, with predominantly behavioral deficits and personality changes. The manifestations encompassed by the construct bvAD substantially overlap with those of the Behavioral variant of frontotemporal dementia (bvFTD). The first specific bvAD criteria were recently published (autumn 2021)¹¹.

Defining cognition

Cognition is defined as mental processes or actions by which we think, comprehend, learn, and remember¹². According to *The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, the cognitive domains are grouped into memory and learning, executive function, complex attention, language, perceptual-motor function, and social cognition (Figure 1)¹³.

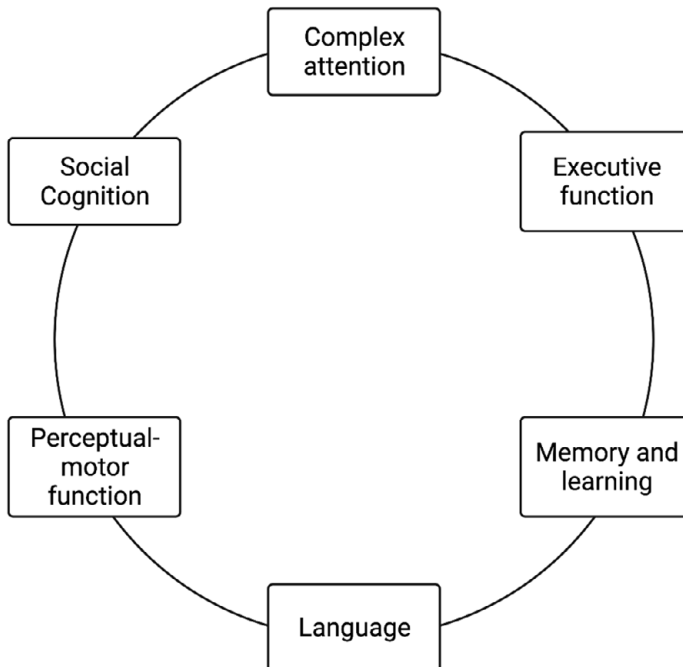


Figure 1. The six cognitive domains according to The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders.

The cognitive abilities rise steeply from infancy to young adulthood, peaks around early middle age and then subtly decreases over the years as part of normal aging^{14, 15}. This senescent decrease is mild and does not affect one's independence in everyday life, whereas cognitive impairment due to ND is accelerated and pronounced¹⁶⁻¹⁸. Most commonly, normal aging affects mental speed, our ability to multi-task, and word finding. However, vocabulary and verbal reasoning often remain unchanged^{14, 15}.

Alzheimer's disease

A historical background

On 25 November 1901, the 51-year-old Auguste Deter (Figure 2) and her husband Karl arrived at the Municipal Asylum for the Insane and Epileptic, in Frankfurt am Main, Germany. The Asylum was located in a spacious gothic building, surrounded by grand gardens. Soon she would become historical as the first case ever described with AD¹⁹.

In the preceding months, there had been a noticeable change in Auguste's behavior. On 18 March 1901, she started groundlessly, and persistently for weeks, to accuse her husband of infidelity with a female neighbor. Retrospectively her husband pointed out this incident as the first sign of what later would come. Soon she displayed progressive memory problems. She grew restless, neglected housework, and developed delusions of an intruding character that wanted to harm her. Furthermore, she spoke of death, became agitated and disturbed neighbors. She purposely hid objects. The situation got out of control. After seeking medical advice, their family doctor recommended her to the local mental institution¹⁹.

Upon admittance, she was closely examined and observed by the psychiatrist and neuropathologist Dr. Alois Alzheimer. The examination of Auguste Deter is well recorded and can be read in the rediscovered medical file²⁰. According to it, the middle-aged woman showed clear signs of progressive cognitive impairment, including memory problems, expressive and comprehensive aphasia, writing difficulties, and disorientation. Beyond these cognitive deficits, there were also notes on psychotic, affective, and behavioral disturbances as portrayed in the following quotes (Auguste Deters words in italic):

“I show her a key, a pencil and a book and she names them correctly. What did I show you? *I don't know, I don't know.* It's difficult, isn't it? *So anxious, so anxious.* I show her 3 fingers; how many fingers? *3.* Are you still anxious? *Yes.*” (Maurer, 1997, p. 1547)²⁰ (Quoted with permission from Elsevier.)

“During physical examination she cooperates and is not anxious. She suddenly says *Just now a child called, is he there?* She hears him calling.” (Maurer, 1997, p. 1548)²⁰ (Quoted with permission from Elsevier.)

“In the afternoon Auguste D. lay in the big main room; in the evening she became unruly. She ran around the room wailing and grabbed other patients' faces so that they, too, became agitated.” (Maurer, 2003, p. 12)²¹ (Quoted with permission from Columbia University Press.)

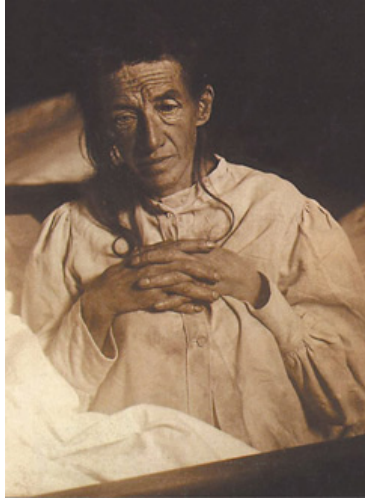


Figure 2. Auguste Deter at the Asylum for the Insane and the Epileptic in Frankfurt am Main, Germany, 1901²⁰. Reprinted with permission from Elsevier©

The last entry in the file by Dr. Alzheimer dates from June 1902:

“Auguste D. continues to be hostile, screams, and lashes out when one wants to examine her. She also screams spontaneously, often for hours...” (Maurer, 2003, p. 22)²¹ (Quoted with permission from Columbia University Press.)

As the years pass at the asylum, Auguste Deter's behavior changes and the agitation subsides. Instead, she spends her days in bed with legs drawn up and is described as “completely stupefied”¹⁹.

On 8 April 1906, Auguste deceases. On histopathological examination, Dr. Alzheimer noted peculiar alterations outside and inside the neurons that later came to be known as amyloid plaques and neurofibrillary tangles, respectively. Dr. Alzheimer had both described the clinical characteristics and discovered key pathological hallmarks of a disease today known as AD²⁰. A century later, it is demonstrated, by a re-examination of the preserved histopathological sections, that Auguste Deter most likely suffered from a rare autosomal dominant variant of familial AD (presenilin-1 gene mutation), with an early and rapid onset of symptoms²².

Taken together, the story of Auguste Deter depicts AD as an illness that goes beyond cognitive symptoms. Affected individuals most often also suffer from non-cognitive mental disturbances, including emotional distress, reduced motivation, psychotic experiences, or changes in behavior. The story further infers that these non-cognitive mental manifestations can appear in various stages of the disease, not only in the later.

A popular clinical description of Alzheimer's disease

Ordinarily, the average AD case is today described as a neurocognitive disorder that clinically starts with subtle, yet slowly progressive, memory problems (e.g., the affected individual forgets where items have been placed or recent conversations). As the disease advances, the memory problems worsen (e.g., forgetting important appointments or names of relatives and repeating oneself)²³⁻²⁷. It is also common with early anxiousness over the impact of these difficulties or worries over an underlying brain disorder²⁵.

In parallel, there is a gradual development of other cognitive difficulties²³⁻²⁶. These include language impairment (e.g., difficulties finding the correct words in speech), learning difficulties (e.g., to learn new facts or develop new skills), apraxia (e.g., difficulties to practically getting dressed or tooth brushing), executive dysfunction (e.g., difficulties with handling devices or planning the day), attention deficits (e.g., being unable to concentrate or being easily distractable) and visuospatial problems (e.g., inability to perceive contrast, speed, or orientation)²³⁻²⁶. Initially these symptoms are mild and can be compensated by other abilities. These mild symptoms are often referred to as MCI. However, when the cognitive deficits have impacted one's functional capacity to such an extent that one's independence in life cannot be sustained, then one has developed the state of dementia¹³. The dementia term is not explicitly used in the context of AD. Hence, dementia can develop due to several diseases compromising the brain.

In the dementia phase, most patients sooner or later manifest BPSD such as anxiety, agitation, aggression, depression, or apathy. There may also occur hallucinations, delusions, wandering, screaming, perseverations, or sleeping disorders. The intensity and duration of these vary widely from case to case²⁴⁻²⁶.

In the more advanced stages of AD dementia, the affected individuals display severe global cognitive impairment and need assistance with most aspects of everyday life. For instance, there are profound difficulties in communicating and orientation. Bodily functions deteriorate, such as the ability to swallow, control of bladder and bowel. Also, the ability to walk is gradually lost^{24, 25}. Many AD patients die from secondary diseases such as pneumonia or cardiovascular disease²⁵. The average survival time from a diagnosis of AD dementia has been approximated to 4-5 years²⁸.

Despite this "typical" clinical presentation of AD, there are significant individual differences in its clinical manifestations and progression, and lately, awareness has grown regarding the importance of also "atypical" profiles²⁷.

Prevalence and impact of Alzheimer's disease

AD is a major and increasing global health concern. As the most common ND, AD contributes up to approximately 50-60 percent of all dementia cases^{29, 30}. It is approximated that more than 50 million people worldwide currently suffer from AD and other dementias²⁶. The strongest risk factor for the development of dementia is aging²⁶. Today we live longer than ever, and the number of people above 65 years of age is expected to almost double by 2050^{26, 31}. Without an effective intervention the prevalence of AD will expand considerably.

As affected persons with AD inevitably worsen in their mental capacities, there is a parallel development of functional impairment, which subsequently renders difficulties in caring for themselves. Consequently, persons with AD grow dependent on others in the management of their everyday life³². Often, the task of caring falls heavily on family members or close friends. In addition to the suffering by patients and caregivers, AD further causes an immense burden on countries' social care systems with significant economic implications. In 2018 the total cost of dementia worldwide was estimated to be one trillion US\$. This figure is expected to rise to two trillion US\$ by 2030³³. Some countries have already reported higher health and social care costs for dementia than cancer and chronic heart disease combined³⁴. Altogether, AD has wide-ranging consequences for patients, families, care systems, and the general society.

Neuropathological hallmarks of Alzheimer's disease

From a neuropathological point of view, AD is associated with three cardinal hallmarks, including accumulation of insoluble extracellular beta-amyloid (A β) plaques and intracellular neurofibrillary tangles (NFTs), later accompanied by neuronal loss and structural brain atrophy (Figure 3)^{30, 35}.

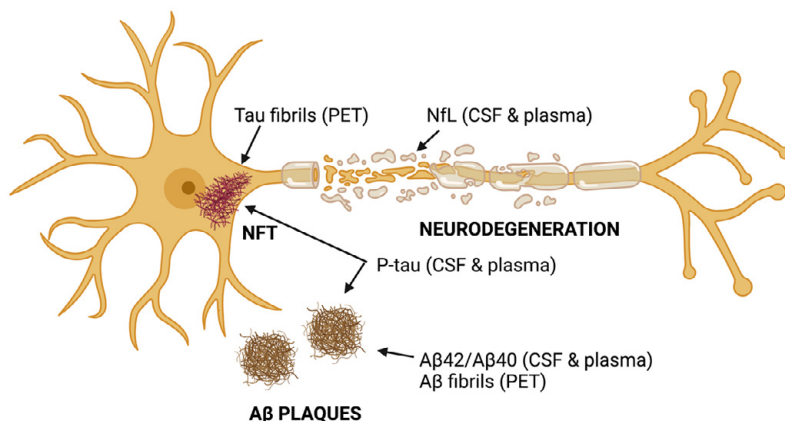


Figure 3. Core Alzheimer's disease pathology and some related biomarkers. Created with BioRender.com

Amyloid plaques

The build-up of A β plaques are thought to arise from an imbalance in A β production or clearance. A β originates from the processing of the transmembrane amyloid precursor protein (APP), richly found in neuronal synapses. APP is proteolytically degraded by two main metabolic routes, the α -secretase pathway and the β -secretase pathway, where the latter is related to the build-up of subsequent A β fibrils^{26, 30}. In the β -secretase pathway, APP is initially proteolyzed by β -secretases (originating from the β -site APP-cleaving enzyme 1) into soluble β sAPP. This degradation is then followed by cleavage by γ -secretases. By these processes, the initial APP molecule is fractionated into free A β peptides that typically contain 37-43 amino acids. The most common isoform is A β 40, whereas the longer peptide A β 42 is more prone to aggregate into oligomers or insoluble fibrils, which cluster and finally form extracellular A β plaques (Figure 3)^{26, 30}. The link between A β and neuronal loss is still under debate, yet the A β oligomers are today thought to play a somewhat superior role compared to A β plaques in causing neurotoxicity³⁵.

Neurofibrillary tangles

NFTs are built up of hyperphosphorylated tau proteins (P-tau). The normal physiological function of tau is to assemble and stabilize the intracellular microtubules, important for the axonal architecture and intracellular transport³⁵⁻³⁷. Accordingly, tau is essential for axonal elongation, morphogenesis, and plasticity^{36, 38, 39}. Hyperphosphorylation results in detachment of tau from the microtubules and consequently creates an increase in the axonal cytoplasmic unbound tau. These unbound compounds of P-tau then aggregate into different shapes and locations^{26, 36, 40}. Aggregates of hyperphosphorylated tau are found inside the nerve cell soma as NFTs, within the neuronal dendrites as neuropils, and extracellularly together with aggregates of A β as neuritic plaques (Figure 3)⁴⁰.

Hierarchy and interplay between core Alzheimer's disease pathologies

The interplay between A β and pathologic tau and how they might cause neurodegeneration is still a source of controversy. According to the widely supported amyloid cascade hypothesis, A β is central in the etiology of AD as an upstream event driving the evolution of pathologic tau, which in turn mediates neurodegeneration, which finally renders clinical manifestations⁴¹⁻⁴⁴.

In support of a hierarchal role of A β , studies on rodents have demonstrated enrichment of tau when A β is injected in the brain tissue⁴⁵. It has also been shown that removal of pathologic tau processes, through genetic knock-out, protects against harmful effects of A β ^{46, 47}. Yet, some animal studies suggest that tau stimulates A β production, and consequently forms pathological feedback loops with accelerated pathological progression⁴⁸.

Humans with hereditary AD, have early onset and rapid decline, and carry autosomal-dominant mutations in the genes encoding for the A β substrate protein APP or the proteolytic presenilin proteins (parts of the γ -secretase complex)⁴⁹. In line, individuals with trisomy 21 (Downs syndrome), which carries an additional copy of chromosome 21 where the APP gene is located, are known to early in life display cerebral A β plaques and clinical AD symptomatology⁵⁰. Biomarker studies have shown that A β accumulation starts ~20 years prior to the development of AD dementia^{51,52}. This advocates that A β is involved very early in the disease processes, yet with only subtle effects on clinical symptomatology, which subsequently infers a mediator variable between the pathological presence of A β and later neurodegeneration and subsequent clinical symptomatology.

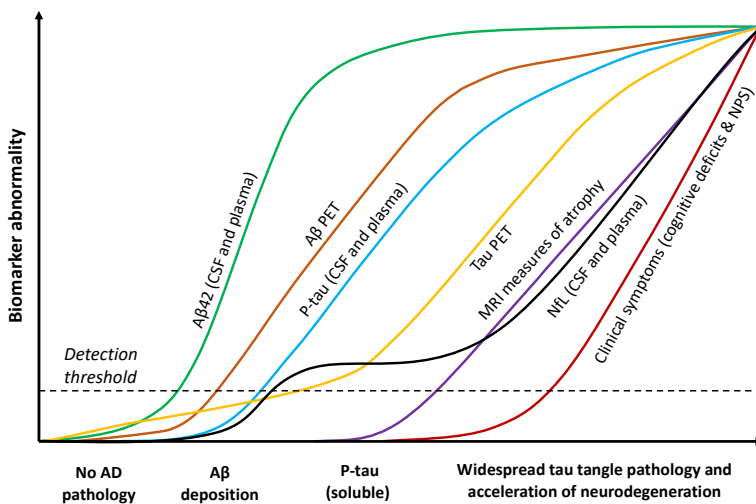


Figure 4. The sequential development of typical Alzheimer disease pathologies and corresponding AD biomarker trajectories. Used and modified by courtesy of Oskar Hansson, Niklas Mattsson-Carlgren and Sebastian Palmqvist

More recent findings on clinical samples instead highlight the presence of pathologic tau to be more strongly associated with neurodegeneration, as well as clinical manifestations (cognitive impairment)⁵³⁻⁵⁷. Also, positron emission tomography (PET) studies have demonstrated that significant levels of pathologic tau are rarely encountered in A β naïve brains⁵⁸, and furthermore that A β is an independent predictor of future tau accumulation in CU subjects^{58,59}. Nevertheless, the upstream molecular mechanisms behind the build-up up of P-tau and NFTs are still unclear and potentially multiplicative since tau pathology is found, not only in AD but also in several other ND³⁶. Interestingly, studies have demonstrated that soluble P-tau species in the presence of A β fibrils mediate the effect by A β on the aggregation of cortical NFTs^{44,60-63}. Combined, these findings favor the sequential development of A β pathology to production, phosphorylation, and secretion of

soluble tau, followed by a sequential growth of NFTs, neurodegeneration, and clinical symptoms (Figure 4)^{42, 58, 64}.

In short, A β could perhaps be designated the “trigger,” while tau could be labeled the “bullet” in the sequences leading up to neuronal dysfunction and clinical AD manifestations⁴⁸.

Spreading of Alzheimer’s disease pathology

Another intriguing aspect of AD pathology is its propagation and spread in the brain. It is speculated that A β and pathologic tau can relocate as seeds from nerve cell to nerve cell by structural connections⁶⁵⁻⁶⁷. In support, *in vitro* studies have demonstrated the capacity of tau aggregates to travel along axons and dendrites as well as to be transferred between neurons through synapses. As such, these pathological compounds appear to progress predominately through highly interconnected brain areas^{37, 66}. Human studies were for a long time limited to *ex vivo* evidence⁶⁷, but already early neuropathological studies suggested that A β and especially tau, on a population level affects brain regions in a stereotypical spatial-temporal pattern³. More recently this evidence has been reinforced by *in vivo* PET studies^{57, 68-70}.

Archetypically, the earliest A β deposits are found in the medial parietal and frontal cortices, including regions such as the precuneus, posterior cingulate cortex, medial- and orbitofrontal cortex (Figure 5 - Panel A). Hereafter, A β is localized in most parts of the human cortex, eventually appearing also in the sensory and motor cortex. Lastly, A β can be demonstrated in the brainstem and cerebellum.

Neuropathological *ex vivo* data^{3, 71} (verified by more recent longitudinal *in vivo* imaging studies^{57, 70}) have revealed that tau on a group level accumulates in the cortex in a quite stereotypic manner according to what is called the “Braak staging scheme” (Figure 5 - panel B). In contrast to A β , tau fibrils in AD are first found in the trans-entorhinal cortex, then typically detected in the amygdala and hippocampus, followed by the presence in other parts of the temporal cortex. Then, tau pathology appears in the parietal and occipital cortex. Finally, tau aggregates in the brain's frontal areas and the motor and sensory cortex³⁵.

Intriguingly, A β and tau pathology have distinct anatomical accumulation patterns. Neuroimaging studies point to an involvement of separate, but nevertheless partly overlapping, functional brain networks^{72, 73}. Initially, A β predominately accumulate in areas involved in the functional default mode network, but also to some extent the frontoparietal network³⁵ - networks thought to play essential roles in cognitive task performance or goal-directed processes, respectively^{74, 75}. However, accumulation of tau seems to map on a wider range of functional networks like the visual, limbic, somatosensory, language, and the frontoparietal networks, as well as to some degree the default mode network^{72, 73}.

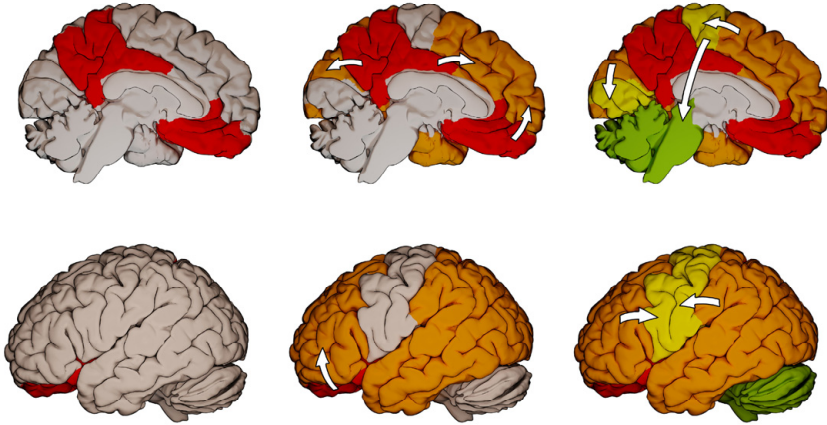
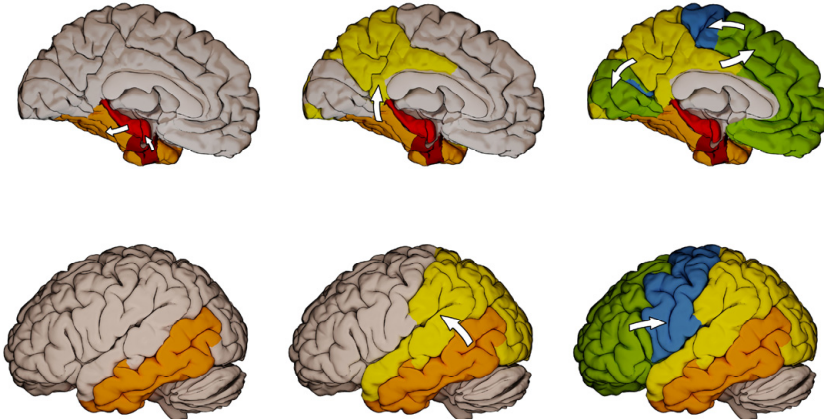
A**A β pathology in Alzheimer's disease****B****Tau pathology in Alzheimer's disease**

Figure 5. Illustrations of the spatio-temporal distribution of A β (panel A) and tau pathology (panel B) in Alzheimer's disease. Arrows and color indicate direction of sequential spread⁷⁶. Used with permission by Springer Nature.

It can be assumed that clinical symptomatology arises in a typical sequential order highly reminiscent of which regions or functional networks that are affected by pathology⁵⁵⁻⁵⁷. AD typically manifests with early impairment in episodic memory, followed by other cognitive deficits, which corroborates well with the spatio-temporal

development of tau pathology^{35, 56}. Yet, clinical observations also support the existence of more rare, atypical clinical presentations of AD, such as the logopenic variant primary progressive aphasia, posterior cortical atrophy, or bvAD^{11,27,77,78}. This questions the consistency of these stereotypic spreading patterns. Also, recent neuroimaging findings have demonstrated a somewhat more heterogenic tau spread according to four different but distinct spatiotemporal patterns (including temporoparietal-, posterior- or medial temporal spreading patterns) with associated distinct cognitive profiles⁷⁹. How these different patterns of tau spread are related to non-cognitive manifestations, such as NPS, remains to be explored.

Biomarkers of Alzheimer's disease neuropathology

Several of the neuropathological changes in AD, including A β and tau pathology as well as neurodegeneration, can today be measured and quantified by biomarkers. Biomarkers are defined as objective indicators (such as physiological, biochemical, or anatomical parameters) of a normal or pathological process, or state, in living organisms⁸⁰. In AD research and clinical settings, biomarkers serve as important and objective ways of studying *in vivo* pathophysiological processes, provide aid in early detection, and predict or monitor disease progression⁸¹.

Biofluid based biomarkers

Molecular abnormalities in the brain can often be detected in the cerebrospinal fluid (CSF)⁸¹, that is a clear, colorless fluid continuously produced by the choroid plexus of the ventricles and the brain parenchyma. Anatomically, the CSF directly surrounds the brain and spinal cord⁸². Given their proximity, chemical compounds and nutrients of the brain are released into the CSF, which can be obtained by lumbar puncture^{81, 82}. Eventually, the CSF and its compounds are reabsorbed by arachnoid granulations into the venous blood system through a pressure-dependent gradient⁸². As a result, both CSF and blood can potentially provide valuable information regarding metabolic processes in the brain parenchyma⁸¹.

One of the more important CSF biomarkers for A β pathology is the A β 42 peptide. In AD, the concentration of A β 42 in CSF is reduced^{35, 81}, this since these peptides are prone to aggregate into A β plaques in the brain parenchyma (Figure 3), resulting in lower concentrations of soluble A β 42 left in the CSF. Low levels of CSF A β 42 are demonstrated to occur decades before the onset of clinical symptoms, as well as before detection using more recent neuroimaging techniques (Figure 4)³⁵. This biomarker is also widely accepted and incorporated in many modern AD diagnostic criteria^{83, 84}.

A β 40 is the predominant form of the A β peptide in the brain, but it does not appear as pathogenic as A β 42. The ratio of CSF A β 42 and A β 40, compared to CSF A β 42 alone, is demonstrated to have several advantages. The ratio results in an even higher concordance with A β pathology (measured by neuroimaging), improved

discrimination of AD dementia vs. other dementias, and higher accuracy in predicting MCI to AD dementia conversion⁸⁵.

In AD, the extent of soluble tau species can be measured in CSF (Figure 3). Increasing levels of CSF P-tau have been shown to reflect both the quantity of A β plaques (in the early stages of disease), as well as NFTs (in the late stages of disease) on PET imaging or neuropathology⁶³. The levels of total tau (T-tau), on the other hand, are assumed to mirror the intensity of neuronal degeneration⁸¹. The use of CSF T-tau and P-tau phosphorylated at threonine181(P-tau181) has extensive literature⁸¹. Considered together with CSF A β 42 or the CSF A β 42/A β 40 ratio, these tau biomarkers are regarded as robust core biomarkers in support of an AD diagnosis and prediction of dementia^{35, 81}. CSF P-tau181 has been shown highly specific to AD and can thus, with high accuracy, discriminate AD from non-AD neurodegenerative disease³⁵. Additionally, levels of soluble P-tau are reported to increase already during the pre-symptomatic phase, when A β fibrils have emerged, but not yet NFTs detectable by PET imaging^{60, 61, 86-88}. Recently, CSF measures of another soluble P-tau species, like CSF P-tau217, has been demonstrated to have a somewhat stronger association with NFTs and outperform CSF P-tau181 in its AD dementia vs. non-AD dementia discriminatory accuracy⁸⁹.

Another important CSF biomarker is neurofilament light chain (NfL)^{35, 81}. Neurofilaments of various sizes are expressed in neurons, especially in their axons, where they play an important role in structural support, axonal growth, and axonal transmission⁹⁰. Increased levels of CSF NfL are found in a variety of neurological diseases such as, Parkinson's disease (PD), multiple sclerosis, vascular pathologies, among others, as well as to some extent in AD and reflect axonal damage (Figure 3)³⁵. Accordingly, the specificity of CSF NfL towards AD is low, yet it is meaningful as a proxy for the level of neurodegeneration and brain atrophy^{35, 81}.

The utility of blood-based AD biomarkers has gained increased attention in recent years. Although CSF AD biomarkers currently are essential in research and clinical management, the development of accurate blood-based biomarkers would have the advantage of being less invasive, requiring less educated personnel and specialized facilities, as well not being as costly. Overall, such a development in diagnostic techniques has the potential to facilitate AD research and intervention trials and enable early disease detection of AD in countries with less advanced health care systems⁹¹. Addressing these needs, P-tau217 has recently demonstrated its promise as such a blood-based biomarker. In one study, P-tau217 in plasma was shown to have a higher or an equally good diagnostic accuracy as established biomarkers⁹². Moreover, plasma P-tau217, in combination with some brief cognitive tests and blood-based genotyping, has further been reported to significantly improve the diagnostic prediction of AD⁹³. Additionally, the less AD-specific biomarker NfL, measured in blood, shows promise as a future tool to detect effects by disease-modifying treatments⁹¹.

Neuroimaging biomarkers

In advantage of fluid AD biomarkers, neuroimaging techniques can provide better spatio-temporal *in vivo* information about A β , tau or neurodegeneration.

PET is a minimally invasive imaging technique where an infusion of a radioisotope labeled ligand binds to a biological target of interest (e.g., cerebral A β deposition). When the radioligand decay, it emits a positron detected by the PET camera. Depending on location and the quantity of the biological target, positrons are sent out in various levels in different anatomical locations, which then can be localized and quantified⁹⁴.

Today there are three clinically approved PET ligands for A β fibrils ([¹⁸F] flutemetamol, [¹⁸F] florbetapir, and [¹⁸F] florbetaben). These have been demonstrated to detect cerebral fibrils with a high accuracy³⁵. In CU individuals, A β -PET has been shown to predict future cognitive decline, and among MCI patients, a positive A β -PET scan constitutes a risk marker for conversion to dementia^{17, 18}. Furthermore, a negative A β -PET in a patient with cognitive impairment essentially eliminates AD as a probable aetiology³⁵. Notably, even if A β -PET positivity on a group level increases the risk of future cognitive decline, many CU individuals with a positive A β -PET scan will not advance to cognitive impairment even after several years of follow-up⁸⁴.

Tau pathology can also be mapped and quantified by PET. Several ligands such as (¹⁸F) flortaucipir, (¹⁸F) MK6240, and (¹⁸F) RO948 have been developed with high affinity to the tau isoforms found in the NFTs in AD (Figure 3)^{35, 95}. Tau-PET has been demonstrated to outperform magnetic resonance imaging (MRI) and CSF biomarkers in separating AD dementia from other ND^{96, 97}. In line with this data, (¹⁸F) flortaucipir has been approved by the U.S. Food and Drug Administration (FDA) for clinical diagnostic use. Compared to both A β -PET and structural MRI, tau-PET has been reported to be more closely linked with early clinical manifestations such as change in cognitive function^{54, 56}.

Structural imaging

In short, MRI is a non-invasive and highly available imaging technique that produces three-dimensional detailed anatomical images by inducing a strong magnetic field together with the addition of radiofrequency pulses. By combining these energies, different “sequences” can be designed with different sensitivity to different tissue characteristics⁹⁸.

Hence, MRI may detect abnormalities in the anatomical structures of the brain. One main clinical advantage with structural imaging is that it can rule out non-AD-related brain disorders like brain tumors, hydrocephalus, or infarcts, which also can cause cognitive impairment. Another comorbidity of importance that can be quantified is the presence of white matter lesions (WML)⁹⁹.

As a proxy for AD-related neurodegeneration, structural MRI allows accurate detection of regional cortical or subcortical atrophy (measured as volume loss or reduced cortical thickness). A large body of evidence supports a stereotypical spreading also for neurodegeneration that maps well on to the Braak staging scheme for tau-pathology^{3, 99, 100}. One of the earliest structures to display atrophy in AD is the entorhinal cortex. Spatially, this is then closely followed by the presence of atrophy in hippocampus, amygdala, and other medial temporal regions, including the inferior temporal, middle temporal, and fusiform cortices (together with the entorhinal cortex by some referred to as the AD-signature cortex). Later the atrophy extends to all parts of the temporal lobe, as well as the parietal and frontal areas of the brain^{99, 100}. As a biomarker for AD neurodegeneration, hippocampal atrophy constitutes one of the most studied. Longitudinal data suggest that hippocampal atrophy precedes dementia with several years, is predictive of AD, and relates to the memory deficits^{99, 100}. However, as neurodegeneration in the medial temporal lobe or hippocampus is commonly encountered also in other ND, such as Dementia with Lewy bodies (DLB) or frontotemporal lobar degeneration (FTLD), the specificity for AD is regarded as low compared to other AD biomarkers¹⁰⁰.

Diagnostic criteria for Alzheimer's disease and cognitive stages

The evolution of Alzheimer's disease criteria

The nosology and diagnostic criteria for AD and dementia have evolved as knowledge has grown regarding their clinical characteristics or pathophysiology, or as *in vivo* biomarker techniques have been advanced.

The word dementia originates from the Latin root *demens* with the meaning “without mind” from the composition *de* [without] and *mens* [mind]). Until Dr. Alzheimer described the case of Auguste Deter, dementia was a loosely defined syndromal concept that covered cognitive impairment as well as behavioral manifestations¹⁰¹. However, after Dr. Alzheimer's histological discovery of cerebral A β plaques and NFTs, the AD construct slowly shifted from being strictly clinical to clinical-biological⁸³. Before the AD biomarker era, the presence of AD neuropathology could only be determined by histopathological examination *ex vivo*, wherefore the *in vivo* identification of the disease nonetheless was restricted to its symptomatology¹⁰². Subsequently, to differentiate the AD dementia syndrome from other conditions (including primary psychiatric disease) and further to increase the specificity of the clinical AD dementia criteria towards AD pathology, the probabilistic clinical criteria were steadily reformulated to center around the cognitive dysfunctions. The behavioral disorders became considered as less important epiphenomena^{101, 102}. With the last decades' remarkable development of *in vivo* AD, the diagnosis of AD has moved from the dementia stage towards the prodromal stages, and the clinical AD criteria have increasingly become biologically oriented with less focus on the clinical syndrome^{83, 103}.

Today, there are several diagnostic criteria for AD, as well as cognitive impairment, in use for both clinical practice and research purposes.

The Petersen criteria for Mild Cognitive Impairment

With growing attention to the early stages of the disease, and as cognitive decline in AD is continuous rather than dichotomous, the concept of MCI has evolved to describe a transitional stage of cognitive impairment that bridges normal aging and early dementia¹⁰⁴. In 1997 Petersen et al. published a set of now widely used criteria which define MCI by i) complaint of defective memory, ii) normal activities of daily living, iii) normal general cognitive function, iv) abnormal memory function for age, and v) absence of dementia¹⁰⁵. These criteria have later been extended by Petersen et al. to cover also mild impairment in other cognitive domains. Three subtypes of MCI are proposed, including *amnestic MCI*, *multiple-domain MCI*, and *single-domain non-memory MCI*¹⁰⁶.

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders

In 2013, an updated set of criteria for AD and the different stages of cognitive dysfunction was published in the DSM-5 by the *American Psychiatric Association* (APA).

In the DSM-5, the term dementia (used in DSM-IV-TR) was changed into *major neurocognitive disorder (NCD)*, while the concept of MCI was represented by the term *mild NCD*¹³.

The DSM-5 manual does not define AD by biology (except if there is genetic proof), and thus it solely rests upon clinical symptoms. The manual uses a two-step method. First, there is an evaluation of whether cognitive impairment is present or not. Second, it is decided whether the cognitive impairment is due to AD or some other disorder¹³.

In short, to fulfill the DSM-5 criteria for major NCD, there should be a significant decline from a previous level of performance in one or more cognitive domains (Figure 1) entailing an interference with independence in everyday activities¹³. The cognitive deficits should neither occur exclusively in the context of a delirium nor be better explained by another mental disorder.

The concept of mild NCD is closely aligned with the MCI construct⁸³. In brief, the DSM-5 criteria include a measurable deficit in at least one cognitive domain, but importantly with relative preservation of functioning¹³.

Hereafter, an AD diagnosis can be established if there is 1) an insidious onset with a gradual clinical decline in one or more cognitive domains (at least two impaired domains if the criteria for major NCD is to be met), and 2) a confirmed causative AD genetic mutation or clear evidence of a decline in memory or learning, and 3)

no presence of any other cerebral disease or condition that explains or significantly contributes to the cognitive decline¹³.

DSM-5 was preceded by DSM-IV-TR¹⁰⁷. However, in this earlier edition a presence of memory impairment in addition to deficits in another cognitive domain was required for the diagnosis of AD dementia. Moreover, the concept of MCI or mild NCD was not included in the DSM-IV-TR.

The National Institute on Aging and Alzheimer's Association Research Framework

In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) published a framework that proposes a strict neuropathological definition of AD. Notably, these criteria are intended for research and not general medical practice⁸³.

The framework centers around fluid or imaging biomarkers *in vivo* or histopathological examination *ex vivo*⁸³. The presence of AD pathology is grouped into those of A β , tau, and neurodegeneration in a corresponding [AT(N)] classification system.

The NIA-AA criteria acknowledge that biomarkers (and the clinical manifestations) develop on a continuum. Accordingly, an individual with the presence of A β deposition alone would be assigned the term *Alzheimer's pathological change*, whereas an individual with both A β and tau deposition would be regarded to have AD. The disease is further staged according to the level of clinical symptoms. Two types of categorical clinical staging schemes are outlined - one "cognitive-syndromal" categorical scheme and one "clinical" numerical scheme.

The syndromal categorical staging scheme divides the cognitive continuum into three stages: cognitively unimpaired (CU), MCI and dementia. CU is defined as a cognitive test performance or clinical presentation within the expected normal cognitive range based on all available information. MCI is defined as a cognitive performance below the expected range, but with the addition that activities of daily living still can be carried out independently. Dementia is described as a considerable progressive cognitive impairment that affects several cognitive domains or neurobehavioral symptoms with evident functional impact on daily living and abates independence.

The clinical numeric staging scheme is only applicable to individuals on the Alzheimer's continuum (positive biomarker designation of either AD or Alzheimer's pathologic change) and reflects the sequential development of AD from established A β positivity in CU subjects to individuals with demonstrated additional tau pathology, neurodegeneration, and dementia.

The International Working Group Criteria

As a response to the biologically oriented NIA-AA criteria, the *International Working Group* (IWG) in June 2021 published an article where they commented on the current limitations of *in vivo* biomarkers in the clinical AD diagnostic criteria and instead recommended continued use of a clinical-biological definition (based on both clinical symptoms and biomarkers) in clinical routine⁸⁴.

The authors argue that a strict biological definition using *in vivo* biomarkers is limited by the too low accuracy of AD biomarkers to predict future cognitive decline in CU individuals, as well as the presence of other brain disorders that can share clinical phenotypes and certain underlying pathologies (e.g., DLB or FTLD).

The recent IWG report instead proposes that the AD diagnosis should be limited to individuals with positive AD biomarkers (amyloid or tau) together with clinical specific Alzheimer phenotypes⁸⁴. The criteria then list a set of common AD phenotypes that include the *amnestic syndrome of the hippocampal type* (argued to be typical), the *posterior cortical atrophy variant*, and the *logopenic variant primary progressive aphasia*. Some more rare AD phenotypes are also mentioned. However, individuals with these should not be a priori classified as having AD, even if the evidence in terms of a positive AD biomarker status is at hand. Instead, AD biomarker-positive asymptomatic individuals are recommended to be classified as being “at-risk for progression”⁸⁴.

The role of neuropsychiatric symptoms in Alzheimer’s disease criteria

Non-cognitive symptoms, such as NPS, have been given modest consideration in modern AD criteria, yet they are not entirely omitted.

In the DSM-5, behavioral and psychological manifestations are acknowledged in the manual as “associated features supporting the diagnoses.” They further state that these are common and distressing. A diagnosis of NCD can also be extended with a specifier of the presence or no presence of a clinically significant behavioral disturbance. Unfortunately, there is no explicit instruction on how these associated features or their specifier are to be operationalized¹³.

The NIA-AA criteria recognize that even if cognitive impairment constitutes core clinical AD criteria, neurobehavioral disturbances, such as changes in mood, anxiety, or motivation, might be prominent features of the clinical presentation. They further recognize the appearance of neurobehavioral symptoms as the first clinical presentation of AD in some individuals. This also justifies their use of the term “clinical staging” rather than “cognitive staging” in their numeric staging scheme. Though, to be classified with high figures in the numeric scheme (corresponding to MCI or dementia in the syndromal staging scheme), individuals must also present with cognitive dysfunction⁸³.

The IWG recommendations do not discuss NPS; instead, they list bvAD as one of the less common AD phenotypes that should not be *a priori* classified as an established AD even if AD biomarker positivity is at hand⁸⁴. Moreover, as the first provisional diagnostic criteria for bvAD were just recently published¹¹, this construct requires further exploration.

Treatment of Alzheimer's disease

At present, AD cannot be cured. All currently approved treatments of AD are drugs that temporarily relieve cognitive symptoms¹⁰⁸. Notably, these symptomatic treatments do not effectively alter the underlying AD disease processes^{108, 109}.

The first group of drugs to be shown efficient as symptomatic treatments of cognitive deficits was the acetylcholine-esterase inhibitors. Today the approved compounds include rivastigmine, donepezil, and galantamine. These drugs operate by strengthening the cholinergic neurotransmission in postsynaptic cortical neurons by inhibiting enzymatic cholinergic breakdown with an ultimately higher amount of acetylcholine in the synapses of the remaining cortical neurons¹¹⁰. The development was based on the cholinergic hypothesis, which suggests that the progressive loss of presynaptic cholinergic cells in the nucleus of basalis Meynert in AD is critical for the development of memory loss and other cognitive dysfunctions¹¹⁰. These treatments are approved to be initiated in mild to moderate dementia^{108, 109}.

The second alternative of symptomatic treatment is an NMDA-receptor antagonist named memantine which protects from the glutamate-mediated neurotoxicity in AD by inhibiting calcium ion-influx^{108, 109}. This drug is indicated for moderate to severe dementia¹¹¹.

For almost one and a half-decade, the research community has energetically searched for effective disease-modifying treatments that can delay or cure the clinical progression of AD. Attempts have been made to interfere with the underlying pathogenic processes. At the moment, there are more than a hundred ongoing trials with the intent of such disease modification¹¹².

Controversially, the FDA in June 2021 approved an A β -antibody (Aducanumab) under their Accelerated Approval pathway, despite the lack of firm evidence of a halted clinical progression. FDA acknowledges that the clinical drug effect is not proven, yet only expected given the demonstrated reduction of A β -plaques¹¹³. In opposite to the decision by FDA, the European Medicines Agency has decided not to approve Aducanumab in clinical practice while awaiting more firm evidence¹¹⁴.

Other degenerative brain disorders

Additional to AD, there are a variety of diseases and conditions that primarily or secondarily affect the brain and result in dementia. In the aging brain, a co-existence of neuropathology is rather the norm than the exception. Hence comorbidity in AD poses a diagnostic challenge and forms a critical confounding factor.

Cerebrovascular diseases

There are multiple cerebrovascular disease states that may underlie vascular cognitive impairment, encompassing major NCD vascular type and vascular dementia (VaD)^{115, 116}. Cortical VaD is predominately caused by large-vessel disease, whereas subcortical VaD predominately is caused by small-vessel disease¹¹⁷. The latter is frequently encountered in middle-aged and older people and associated with demyelination of the neuronal fibres¹¹⁸⁻¹²⁰. Demyelination due to vascular pathology can be visualized on T2 weighted and fluid-attenuated inversion recovery (FLAIR) sequences on MRI as white matter hyperintensities (referred to as WML)^{116, 121}.

The presence of WML increases with age and the number of cardiovascular risk factors such as untreated blood pressure, dyslipidemia and diabetes^{120, 122}. Yet, WML also has non-vascular underlying causes such as inflammation, genetic causes, toxic agents, and some metabolic deficiencies^{116, 121, 123}.

The precise cognitive impairments associated with WML differ according to the extent and location, but commonly share a profile with slowing of mental and motor processes and executive dysfunction^{115, 117}.

Parkinsonian disorders

PD is the second most prevalent ND¹²⁴. PD is a movement disorder with bradykinesia, resting tremor, rigidity, and postural and gait instability as cardinal manifestations. However, there are also a wide array of non-motor symptoms, including cognitive impairment and neuropsychiatric manifestations^{125, 126}. More than 75% of the affected individuals will develop dementia after ten years of disease duration¹²⁷.

A key pathological hallmark is the presence of α -synuclein aggregates as intraneuronal Lewy bodies or neurites that are thought to first appear in the dorsal motor nuclei of the vagus nerve or the olfactory bulb and then spread to the brainstem, basal ganglia, and the neocortex¹²⁸. The characteristic motor symptoms (and some of the non-motor symptoms) are thought to arise due to the pathological loss of dopamine-producing neurons in the substantia nigra pars compacta¹²⁵.

Another α -synuclein-related disease is DLB. However, in comparison to PD, DLB displays more cortical engagement, and another important distinguishing feature is the timing of the cognitive deficits. In DLB, the cognitive impairment typically

precedes the parkinsonian motor symptoms¹²⁹. In contrast to AD, PD and DLB display more cognitive fluctuations, executive dysfunction, more prominent visuospatial difficulties, as well as worse attention deficits^{129, 130}.

There are also other rarer ND with parkinsonian symptomatology, such as Corticobasal degeneration (CBD), Progressive supranuclear palsy (PSP), and Multiple system atrophy. While Multiple system atrophy also is another α -synucleinopathy, CBD and PSP are primarily regarded as *tauopathies* with other tau isoforms than encountered in AD¹³¹.

Frontotemporal lobe degeneration

FTLD is a leading cause of dementia before 65 years of age¹³². FTLD is classified into three clinical variants: bvFTD, *the non-fluent variant primary progressive aphasia*, and the *semantic-variant primary progressive aphasia*. bvFTD accounts for approximately 60% of the FTLD cases, and its most pronounced early symptoms include personality changes, disinhibition, and apathy^{132, 133}. However, also psychotic symptoms and personality change may occur¹³⁴. Hence, these behavioral disturbances can easily be mistaken for primary psychiatric disorders, such as depression, personality disorders, schizophrenia, bipolar disorder, or vice versa¹³⁴⁻¹³⁶.

The FTLD neuropathology grossly encompasses neuronal loss and gliosis in the frontal and temporal lobes. However, the more detailed underlying pathological changes are complex and include, e.g., various forms of tau pathology, TAR DNA-binding protein 43 (TDP-43) inclusions and fused in sarcoma protein pathology. Some of these pathologies are thought to arise due to genetic mutations¹³⁷. A common mutation in FTLD is the expansion of the C9orf72 gene^{135, 137}.

Limbic-predominant age-related TDP-43 encephalopathy

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a disorder in older adults that has recently been recognized as a unique clinical entity¹³⁸. The prevalence of LATE has been reported to be more than 20% in individuals above 80 years of age¹³⁸. Clinically LATE mimics the amnesic difficulties seen in Alzheimer's disease, although it shares the presence of TDP-43 pathology with FTLD^{138, 139}. Hippocampal sclerosis is often present in those displaying the disorder^{138, 139}.

LATE is distinguished from FTLD by its late onset as well as the anatomically restricted pathology. Yet, at present, LATE pathology can only be confirmed at autopsy, hampering the clinical utility¹³⁸. The proteinopathy is staged according to its anatomical distribution, and the pathology is believed to start in amygdala and then progress to hippocampus, followed by other temporal structures¹³⁸.

From a NPS point of view, the initial build-up of pathology in amygdala is interesting as this limbic structure is thought to play an essential role in emotions

and motivation¹⁴⁰. However, even if there is some evidence of a link between LATE and NPS¹⁴¹, others have displayed a lack of such an association¹⁴².

Primary Age-Related Tauopathy

For almost two decades, it has been known from autopsy studies that accumulation of P-tau can be detected in the brains of cognitively healthy young adults without the presence of A β pathology. This accumulation, of disputed significance¹⁴³, predominately develop in the noradrenergic brain stem nucleus locus coeruleus, and this is well before NFTs appear in the transentorhinal cortex and other temporal structures¹⁴⁴⁻¹⁴⁶. Additionally, other post-mortem studies have reported individuals with a typical clinical AD profile to have only minimal or null cerebral A β plaques yet abundant NFTs¹⁴⁷⁻¹⁴⁹.

To put light on this controversy with the classical literature on AD pathology, the concept of Primary Age-Related Tauopathy (PART) was formulated. Correspondingly, the concept of PART reflects upon this presence of cerebral AD-like NFTs, but with only a little or no A β deposition^{149, 150}.

The impact on cognition is discussed, yet most studies indicate that the cognitive decline in PART is mild and rarely progresses to dementia¹⁵⁰.

Neuropsychiatric symptoms

Prevalence and recognition of neuropsychiatric symptoms

Individuals that eventually develop AD dementia almost inevitably develop one or more NPS at some point during their disease course^{4, 5, 151, 152}.

In the population-based longitudinal Cardiovascular Health Study, the prevalence of any NPS among demented individuals was 75%. The most common NPS was apathy (registered in 36%), closely followed by depression (registered in 32%).

However, NPS was also frequently encountered in the prodementia stages. In the same population-based study, 43% of the individuals with MCI and 16% of the CU older adults reported NPS⁵. Apathy or depression was also in these earlier stages the most prevalent conditions among the various NPS¹⁵³. Anxiety symptoms were present in 10% of those with MCI and 6% among CU⁵. Similar prevalence rates in non-demented stages have been described in the population-based Mayo Clinic Study of Aging⁴. Moreover, most cognitively impaired individuals display several NPS at once, with cumulative functional impact¹⁵⁴.

Besides addressing NPS as early findings, these prevalence studies highlight that the frequency of NPS rise with worsening cognition. As such, NPS and cognitive impairment in AD could be assumed to develop in parallel. Yet, the time of the first

onset of NPS, and the onset in relation to cognitive impairment, during the very earliest stages have rarely been investigated¹⁵⁵.

Clinically, NPS have been depicted as underrecognized or overlooked during the diagnostic phases in memory clinics^{8, 156-158}. It is also reported that approximately almost every fourth AD patient has received a prior psychiatric diagnosis before their ultimate clinical diagnosis of AD¹⁵⁹. This suggests a risk of misclassification and subsequent delayed management, underpinning the importance of acknowledging the link between NPS and AD.

Adverse outcomes of neuropsychiatric symptoms

NPS serves as an important factor in the development of difficulty or distress among patients and their caregivers.

As the inability to uphold one's independence in living is key in establishing a dementia diagnosis, appraisal of functional deficits is essential. Loss of function is often presumed to be predominantly driven by cognitive impairment in AD. However, also certain NPS, such as apathy or anxiety, have been demonstrated to be significantly associated with functional deficits^{151, 160-163}. Notably, this association has further been shown independent of cognitive impairment^{161, 164}.

As individuals affected by AD grow increasingly dependent, help is often provided by family members or friends, and eventually, many require institutionalization. However, caring is usually a demanding and stressful undertaking. A high caregiver burden has been shown present already during the early stages of disease¹⁶⁵⁻¹⁶⁷, and associated with an elevated risk of psychiatric morbidity¹⁶⁸. Consistently, NPS, rather than the cognitive deficits, has been shown to be a major contributor of not only an increased caregiver burden^{32, 169, 170}, but also an earlier institutionalization^{154, 171-173}.

Further strengthening the importance of NPS, reduced quality of life in mild to moderate AD dementia has consistently been shown associated with increased levels of affective disturbances, but not cognitive test performance¹⁷⁴⁻¹⁷⁷. Similar findings have been reported in the non-demented stages of AD¹⁷⁸. Finally, NPS have been found noteworthy drivers of health care costs^{179, 180}.

Definitions of apathy, depression, anxiety, and mild behavioral impairment

Definitions and criteria for apathy

The term *apathy* has its origin in the Greek word *apatheia*, derived from the adjective *apathēs*, meaning “without feeling” or “without passion”¹⁸¹. In ancient Greek society, the Stoic philosophers considered apathy to be a virtue necessary to achieve a righteous and happy life. In their opinion, emotions undesirably interfered

with rationality and other reasoning cognitive abilities, and hence emotions ought to be dismissed. Over time the concept of apathy has shifted from a desirable state of mind to its modern medical concept, where apathy is viewed as a behavioral impairment¹⁸².

In the early 1990s, a medical definition of apathy was introduced by Dr. Robert Marin^{183, 184}. The definition has become widely recognized and depicts apathy as a psychiatric syndrome with a diminished motivation not attributable to a reduced level of consciousness, cognitive impairment, or emotional distress. Dr. Marin further proposed diagnostic criteria, which in short encapsulate 1) lack of goal-directed behavior, 2) reduction in goal-directed cognition, and 3) lack of emotional responsiveness¹⁸⁴. Dr. Marin operationalized diminished goal-directed behavior as an absence of effort, initiative, or productivity, whereas lowered goal-directed cognition was anchored in a reduced interest, lack of plans or goals, or lack of concern about one's wellbeing. Reduced emotional concomitants of goal-directed behaviors were operationalized as blunted affects, emotional indifference, and limited responses to significant life events^{182, 183}. These criteria have since, by others, been revised in 2009 and 2018^{185, 186}.

According to the most contemporary definition, apathy is characterized by a set of criteria (A to D) proposed by an international working group 2018¹⁸⁶. Criterion A states that there must be a quantitative reduction of goal-directed activities compared to the affected individual's previous functioning. Criterion B states that the manifestations must exist for at least four weeks and further affect at least two out of the three apathy dimensions covering diminished goal-directed behavior or activities (including loss of interest), diminished emotions, or diminished engagement in social interaction. Support of an "affected" dimension rests upon several provided examples or situations for each domain. The symptoms should further trigger clinically significant impairment in personal, social, occupational, or other important areas of functioning to meet criterion C. Criterion D stresses that the apathy symptoms should not exclusively be explained by physical disabilities, motor incapacities, altered consciousness or substance use, or a major change in the environment of the patient¹⁸⁶.

Apathy is not considered a separate psychiatric entity or defined by the DSM-5. Instead, apathy is only mentioned as a "behavioral disorder" in mild or major NCD, as a "symptom" of FTLD, and further as a "personality change" due to "another medical condition"¹³.

Definitions and criteria for depression

In the general public, the essence of the term *depression* is described as a *state of feeling sad* or as a *medical condition in which a person feels sad, hopeless, and unimportant, and often is unable to live in a normal way*¹⁸⁷. The leading medical definition of depression is provided by the DSM-5¹³.

The criteria in DSM-5 for major depression outlines that the individual must present with either 1) depressed mood or 2) loss of interest or pleasure (anhedonia), and in addition fulfill three or four associated criteria such as a significant unintentional weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, or recurrent thoughts of death. The symptoms must be present (most of the day, nearly every day) during the same two-week period, represent a change from previous functioning, and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms should also not clearly be attributable to another medical condition or physiological effects of substance¹³.

Another widely used set of criteria for depression is provided by the World Health Organization in the *tenth revision of the International Classification of Diseases (ICD-10)*¹⁸⁸. The DSM-5 and ICD-10 criteria share several features. However, the main difference between them is that ICD-10 uses three cardinal criteria (including depressed mood, loss of interest or pleasure, or reduced energy) instead of only the two used in DSM-5. In ICD-10, two out of these three typical symptoms ought to be present to determine the diagnosis¹⁸⁸.

These modern concepts of depression have evolved from early diagnostic theories of melancholia in a complex process spanning decades of scholarly work¹⁸⁹⁻¹⁹². In the 1970s, when the *Research Diagnostic Criteria* for major depression were outlined, the distinction between depression and melancholia was eliminated. Hence, the major depression criteria “loss of interest or pleasure” (anhedonia), which is considered essential for the construct of melancholia, was upgraded to constitute not only an associated criterion but also to become one of the current core criteria for major depression. These Research Diagnostic Criteria were later used as the foundation when developing the succeeding DSM-III diagnostic criteria during the 1980s, criteria that have remained essentially unchanged ever since^{191, 193}.

The clinical utility of the concept “depression” is indisputably supported by its historical staying¹⁹⁰. Nevertheless, the concept has been criticized for its polythetic syndromic definition resulting in a high diagnostic heterogeneity. For instance, it has been calculated that there are 227 possible theoretical ways to meet the criteria for major depression¹⁹⁴. Adding to the diagnostic uncertainty, there are also several other overlapping mood disorders according to the DSM-5 framework, e.g., persistent depressive disorder (dysthymia), bipolar disorder, and cyclothymic disorder¹³. Furthermore, there are also some proposed less established constructs of depression among older adults or in the context of neurodegenerative disease. Late-life depression (LLD) or geriatric depression refers to depressive syndromes as they are defined in DSM-5 or ICD-10; however, they arise in adults older than age 65 years¹⁹⁵. Other proposed constructs are minor depression and subsyndromal depression, which refer to the concept of major depression, yet only two (but fewer than five) diagnostic symptoms are required^{195, 196}.

Attempts have also been made by the *National Institute of Mental Health* to establish criteria for depression in AD^{197, 198}. These were based on the DSM-IV criteria for major depression and AD¹⁰⁷. The main distinctions from the original major depression criteria are that the numbers of criteria that need to be fulfilled were changed from five to three and that these symptoms need to be present together within the same two-week period. Additionally, the “diminished ability to think or concentrate” was removed due to its expected low specificity in this often cognitively impaired sample. Also, the criteria encompassing anhedonia (loss of interest or pleasure) were altered to “decreased positive affect or pleasure in response to social contacts and usual activities.” Two additional criteria were further added, including “social isolation or withdrawal” and “irritability.” The utility of these criteria has hardly been investigated, but some reports indicate that these criteria designate a greater proportion of AD patients as depressed^{199, 200}.

Definition of anxiety

The word *anxiety* is etymologically linked to the Latin *ango* (to constrict) and *angustus* (narrow) and primarily denotes a distressing emotional state of the mind²⁰¹. The modern, straightforward definition of the word is a *fear or nervousness about what might happen*²⁰². The DSM-5 framework nuances this by defining anxiety as an expectation of a future threat, while the term *fear* is defined as an emotional response to a real or perceived imminent threat. Moreover, DSM-5 describes the term “worry” as the cognitive aspects of anxious anticipation²⁰¹.

Medical practice mainly confines work to abnormal or pathological phenomena. However, defining boundaries between a normal psychological reaction of a stressor and pathological anxiousness is difficult. Nonetheless, besides the anxiousness being excessive or severe, the main divider between a “normal” anxious reaction and an anxiety disorder is that the latter usually causes clinically significant distress or impairment in several parts of life. Also, the reoccurrence is more frequent, and the duration is longer for anxiety disorders than what is considered normal¹³.

DSM-5 lists several types of anxiety disorders, including generalized anxiety disorder, panic disorder, specific phobias, agoraphobia, social anxiety disorder, and separation anxiety disorder¹³. However, most AD studies do not address the link to these separate constructs, but have instead investigated the impact by anxiety severity, regardless of type²⁰³. In science, anxiety is commonly also separated into *state anxiety* and *trait anxiety*. The former is activated in response to a certain stressful setting, while trait anxiety refers to an overtime relatively stable personality that increases the likelihood of entering an anxious state. The personality trait *neuroticism* is closely aligned with the concept of state anxiety. The role of state anxiety or neuroticism in AD has been explored in some studies^{204, 205}.

Definition and criteria for Mild Behavioral Impairment

Behavioral symptoms have for long been acknowledged as important early manifestations of bvFTD, and hence the concept of MBI was first introduced in such a scientific setting²⁰⁶. However, behavioral or psychiatric symptomatology has been reported to constitute early manifestations prior to cognitive complaints also in other ND such as AD^{159, 206, 207}. Therefore, it was articulated a need to expand the initial MBI concept to encompass all ND. Accordingly, a working group, originating from the NPS *Professional Interest Area* of the *International Society to Advance Alzheimer's Research and Treatment* (ISTAART), was founded in 2012 to develop new MBI criteria, published in 2016¹⁰.

The new MBI criteria were founded on the already described assumption that personality change, behavioral, or psychiatric symptoms are early manifestations of various ND, and further that these can appear in advance of cognitive impairment. Moreover, the criteria emphasize that the type of the initial manifestation depends on the pathology's sort or location.

The concept is restricted to late-life (>50) onset of psychiatric symptomatology, which should persist intermittently for at least six months and represent an evident change from the individual's normal behavior or personality. The manifestations should further not be attributable to another current primary psychiatric disorder. Importantly, the MBI criteria allow, but do not require, coexistent MCI. However, NPS emerging after dementia onset are not regarded as MBI. The concept includes five domains of various MBI types, including disturbances in motivation, affective regulation, impulse control, social cognition, and perception/thought content¹⁰.

The overlap between apathy, depression, and cognitive impairment

The concept of apathy indisputably overlaps with the concept of depression (Figure 6)^{208, 209}. The conditions also frequently co-occur⁵. Cognitive deficits in AD can further be misinterpreted as apathetic or depressive symptoms or vice versa²⁰⁷. Altogether, this poses a significant diagnostic challenge that corroborates well with the report that many patients have received a primary psychiatric diagnosis before the final diagnosis of AD¹⁵⁹.

Nevertheless, apathy is in general acknowledged as a distinct psychiatric entity, independent from depression^{184, 208, 210}. Phenomenologically, apathy is more strongly related to blunted emotions and motivational loss¹⁷⁶, whereas depression encompasses a distressful emotional state. However, as “loss of interest or pleasure” has attained an up-lifted position as main criteria for major depression¹³, it inevitably becomes a challenge to separate apathy from depression.

Also, attention deficits and other cognitive impairments frequently encountered in AD have proximity to the depression criteria “diminished ability to think or concentrate.” The low persistence in performing tasks for apathetic individuals can be mistaken for depressive or cognitive difficulties to concentrate. AD patients also

often exhibit difficulties in cooking and forget to eat, which subsequently lead to “loss of weight,” which is another associated criterion for major depression. Somewhat similar, AD patients frequently complain about fatigue, which can be explained by their efforts to deal with their cognitive difficulties, and corresponds to the depression criteria “insomnia or hypersomnia.” Usually individuals with AD are regarded as having a behavior reflecting a lack of interest, without fulfilling the full criteria for apathy. Perhaps this can be explained by abstaining from struggling with tasks they know they cannot accomplish.

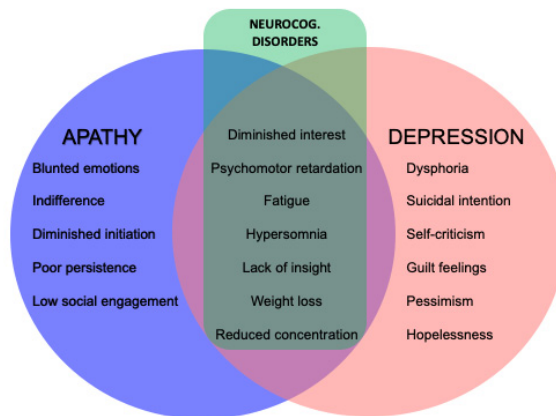


Figure 6. The theoretical overlap between apathy, depression, and certain symptoms related to neurocognitive disorders.

The relationship between neuropsychiatric symptoms, cognitive impairment, and Alzheimer’s disease neuropathology

The interplay between NPS, cognitive impairment, and AD-related pathologies is complex, and up to this time, their exact casual and temporal relationships remain unclear, especially during the early stages of disease²¹¹. The following sections aim at outlining the main findings in the current literature. However, the heterogeneity between findings is great, probably reflecting diverse definitions, as well as other methodological challenges.

Modeling the relationships

There are several hypothetical models to explain the links between NPS, cognition, and AD-related pathology²¹².

First, an association between NPS and cognitive impairment could be explained by NPS giving rise to the cognitive deficits (Figure 7, arrow a). For instance, anxiety

or other strong emotional experiences could occupy prefrontal and temporal functions such as attention and episodic memory^{213, 214}.

Second, cognitive deficits might induce NPS (Figure 7, arrow b). For example, a psychological worry or anxiety could develop because of cognitive symptoms inferring the presence of a potentially serious neurological disease.

Third, both cognitive impairment and NPS could arise from underlying AD pathology (Figure 7, arrow c), if for instance, brain structures related to memory (e.g., hippocampus) or emotions (e.g., amygdala), respectively, are damaged (Figure 7, arrow d & e).

Fourth, the relationship between NPS and AD pathology could also be bidirectional, with NPS exerting a causal effect on AD pathology or resilience factors against cognitive decline (Figure 7 – arrow b & f). Recurrent depression early in life has been demonstrated related to longstanding hypercortisolism, suggested to cause neurotoxicity with subsequent hippocampal atrophy, increasing the risk of clinically significant memory impairment if AD pathology also develops²¹⁵.

These models are not mutually exclusive, on the contrary, likely all these models are in play. However, the degree of their contribution to the clinical presentation possibly varies over the disease course.

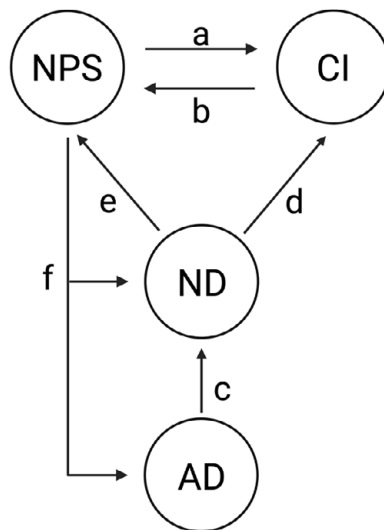


Figure 7. A hypothetical model on the relationship between AD-related pathologies, cognitive impairment, and neuropsychiatric symptoms. Arrows indicate a hypothetical causal effect. a) NPS causes CI, b) CI causes NPS, c) AD-related pathologies cause neuronal dysfunction, which depending on location, gives rise to CI (d) or NPS (e). f) Early-onset long-term NPS cause effects on the development of AD-related pathologies or neuronal dysfunction. Abbreviations: AD = Alzheimer’s disease related pathology, CI = Cognitive impairment, ND = neuronal dysfunction, NPS = Neuropsychiatric symptoms.

Neuropsychiatric symptoms as risk markers for cognitive impairment

There is mounting evidence that NPS already in CU older adults or patients with MCI constitute harbingers for subsequent cognitive impairment or dementia.

Several large-scaled studies have consistently demonstrated that the overall burden of NPS, as well as some specific NPS, increase the risk of conversion from CU to MCI or from MCI to dementia²¹⁶⁻²²⁰. In one of them, agitation, apathy, and anxiety were found to be risk markers of incident MCI at a similar or greater magnitude as neurodegenerative findings on structural MRI²¹⁷. In line, the construct of MBI has been reported to be at least as strong risk marker for progression to MCI or dementia as subjective cognitive decline²²¹. However, the impact by NPS on more continuous measures of cognition is less studied. Nonetheless, two recent population-based studies on non-demented subjects reported NPS to affect the longitudinal cognitive trajectories with accelerated decline^{222, 223}.

Intriguingly, a recent longitudinal study on >1 500 A β -positive subjects on various stages of AD found neither evidence for a cross-sectional association between NPS and cognitive functioning in the early stages of the disease nor demonstrated NPS as a significant driver of cognitive decline⁶. These results contrast much of the previous literature and might be due to their sample selection. Previous studies have rarely used biomarker evidence of AD and have instead mainly based their recruitment on cognitive staging. In such samples, focusing on early stages of disease (CU or MCI), the presence of NPS might be indicative of an underlying AD pathology. As the authors themselves suggest, in this particular study, they had already increased the probability of future cognitive decline by restricting the inclusion to A β -positive cases. NPS may therefore have had a relatively low added predictive utility for future cognitive deterioration⁶.

Apathy as a risk marker for cognitive impairment

Apathy has consistently been linked to cognitive deficits and a higher risk of conversion to MCI or dementia in non-demented older adults²²³⁻²²⁵. A meta-analysis study comprising 7 365 participants from 16 studies report apathy in MCI to be associated with an approximately 2-fold risk of dementia²²⁴. In one of the included studies, a criteria-based diagnosis of apathy in MCI increased the risk of AD dementia almost sevenfold. In opposite, a diagnosis of major depression did not²²⁰. Apathy has further been linked to lower test performance in several specific cognitive domains²²³. Yet, its strongest association is probably with executive dysfunction²²⁶⁻²²⁸. Maybe this is explained by an overlap in the theoretical frameworks of these constructs, as both apathy and executive dysfunction encompasses the inability to stay on and complete tasks or take initiative^{186, 229, 230}.

Anxiety as a risk marker for cognitive impairment

Altogether, the literature seems to support the role of anxiety as a risk marker for cognitive impairment. First, a personality trait of neuroticism early in life has been demonstrated to constitute a risk marker for AD dementia^{204, 231, 232}. Second, anxiety also in older adults (with or without MCI) is reported as a risk marker for both cognitive decline and AD dementia^{216, 217, 233-237}. In a large longitudinal study comprising over 12 000 CU older adults, anxiety has been found to predict AD dementia with a hazard ratio >3 ²³⁶. In another study, $>80\%$ of the MCI participants with co-morbid anxiety developed a clinical AD diagnosis within three years. The corresponding figure for those with solely MCI was 40% ²³⁷. Third, anxiety has also been found to interact with A β in non-demented individuals, resulting in an accelerated cognitive decline²³⁸. Combined, these findings align with previous cross-sectional studies demonstrating an association between anxiety and impairment in specific cognitive domains such as memory performance and complex attention.^{239, 240}

Depression as a risk marker for cognitive impairment

The role of depression as a risk marker has been debated for decades²⁴¹. A large meta-analysis has reported participants with depression to have 1.3 times higher risk of conversion from MCI to dementia²⁴¹. Also, increased depressive symptoms among CU older adults have been reported to negatively impact the longitudinal trajectories of cognitive test performance^{223, 242}. Another study has demonstrated a graded relationship between depression severity and the future risk of dementia, where a higher level is associated with higher risk²⁴³. However, many studies have also failed to display associations between depressive symptoms and forthcoming cognitive deterioration^{220, 222, 244, 245}. The divergent findings can probably be accounted for by heterogeneous methods and definitions, some of which indeed also apply to other types of NPS studies.

Cognitive impairment as a risk marker for neuropsychiatric symptoms

Only a few studies have addressed the impact of cognition on longitudinal NPS in ND²⁴⁶⁻²⁴⁸. In a follow-up study on CU older adults, neither cognitive test performance nor retrospective informant ratings of cognitive change exerted effects over time on apathy²⁴⁶. In contrast, it has been reported from a more recent longitudinal study on CU older adults that attention deficits were related to chronic elevated subsyndromal depressive symptoms, whereas executive dysfunction was linked to moderately elevated trajectories of long-lasting anxiety²⁴⁸. Interestingly, the global cognitive function has been demonstrated to mediate the association between core AD pathologies and anxiety or apathy²⁴⁷. Of note, these latter findings rest upon cross-sectional data, making it difficult to draw firm conclusions on the direction of these findings.

The relationship between Alzheimer's disease pathology and neuropsychiatric symptoms

Efforts have also been made to unravel the link between AD-related pathologies and NPS. During the last decade, the field has shifted focus from late clinical (dementia) to preclinical (CU) or prodromal stages (MCI) of AD²¹¹. Overall, there are trends supporting associations between neuropathology and certain NPS already during these non-demented stages²¹¹. However, given inconsistencies between reports, a definite neurobiological signature has yet to be established²¹¹. The width of the methodological approaches is also here considerable and can potentially account for some of the conflicting reports.

Addressing the overall burden of NPS, the global level of cerebral A β deposition has been cross-sectionally linked to increased MBI levels among CU older adults²⁴⁹. In line, a recent longitudinal study, also addressing CU individuals, demonstrated biomarkers for both A β and tau pathology to predict longitudinal increases in the overall change in mood (including depression)²⁵⁰. However, the follow-up was restricted to only one year.

The relationship between Alzheimer's disease pathology and apathy

Several PET and CSF studies support an association between A β and apathy²⁵¹⁻²⁵⁵. In a recent large-scaled longitudinal study on non-demented stages of disease, individuals with apathy, compared to those without apathy, demonstrated an elevated cerebral A β deposition as well as an accelerated cognitive decline. Besides, the effect of apathy on cognitive function was mainly mediated by A β deposition in prefrontal areas of the brain²⁵³. In support, also another study has related apathy to A β deposition in the prefrontal cortex, and then especially so in the orbitofrontal gyrus and the left superior frontal gyrus²⁵¹. Further supporting an association, a CSF study on AD demented individuals report levels of CSF A β 42 to be negatively (i.e., more pathological) correlated with apathy rating scores (i.e., higher level)²⁵⁴. Additionally, a large-scale longitudinal study, spanning over five years, demonstrated individuals with low CSF A β 42 on a group level to have steeper increases in apathy scores over time²⁵⁵.

Yet, some CSF and PET studies do not support a role of A β in apathy²⁵⁶⁻²⁵⁹. Also, most neuropathological studies have reported apathy not to be related to the amount of A β plaques at autopsy²⁶⁰⁻²⁶². However, these latter studies are mainly small sample-sized and address predominately later stages of disease.

Contrary to A β , most neuropathological studies do display an association between tau and apathy²⁶⁰⁻²⁶². These findings are supported by a cross-sectional CSF study on mild AD dementia that reported apathy levels to be associated with increased levels of both CSF T-tau and P-tau²⁵⁶. In another CSF study, a low level of A β combined with a high level of tau (i.e., more AD pathology) was longitudinally

associated with an increased probability of increased future apathy scores. Yet, tau was not associated with increasing apathy scores over five years of follow-up independent from A β ²⁵⁵. Moreover, several other CSF studies (predominately cross-sectional), encompassing early to late stages of AD, do not relate apathy to P-tau^{254, 257, 258}.

Opposing these negative CSF studies, a few cross-sectional and longitudinal tau-PET studies have displayed associations between apathy and tau pathology²⁶³⁻²⁶⁵. In a study on MCI and AD demented individuals, apathy was related to tau pathology in small frontal parts of the cortex, including the anterior cingulate and the dorsolateral prefrontal cortex. Notably, the associations were more robust in individuals with greater A β pathology²⁶³.

Most reports on apathy favor an association with neurodegeneration^{155, 247, 266-268}. In the late stages of the disease, cortical atrophy is found predominately in frontal brain regions (including the medial frontal cortex, the orbitofrontal cortex, or the anterior cingulate cortex) and subcortical structures such as the caudate, putamen, and thalamus^{155, 266, 267}. These are structures suggested to be a part of the neurocognitive network of normal motivated behaviour²⁶⁹. In early stages, however, there are suggestive findings also arguing for a role of temporal atrophy²⁶⁸, brain structures known to accumulate tau tangles early on³.

The relationship between Alzheimer's disease pathology and depression

Several cross-sectional CSF studies, encompassing various stages of the disease, do not display an association between depressive symptoms and the level of amyloid pathology^{256, 257, 270-272}. Also, several PET studies align with these results²⁷³⁻²⁷⁵.

Notably, many studies even display depression related to reduced levels of A β pathology^{270-272, 276}. Such a finding was reported by a recent PET imaging study on CU and MCI individuals with or without LLD²⁷⁶. Beyond demonstrating reduced A β pathology in LLD individuals, both A β and depression were independently associated with poorer memory performance. These findings strengthen the notion that depression late in life, by its impact on cognition, could play a role in demasking an incipient AD by lowering cognitive resilience factors, rather than being associated directly with increased A β levels.

However, challenging these negative results, there are also many PET studies supporting an association between A β and depression^{153, 250, 277-281}. Some have assessed depression severity by the Geriatric Depression Scale (GDS). One study, on CU subjects, displays steeper rates of total scores on the GDS over time for participants with higher levels of cerebral A β deposition at study start²⁸⁰. According to their sub-analysis in which the three item-clusters of the GDS scale (dysphoria, anxiety-concentration, and apathy-anhedonia, respectively) were analyzed, the average dysphoria item-cluster score was demonstrated lower than the other item-clusters scores. Besides, change in dysphoria was not related to A β at study start.

Somewhat similar results using the GDS are reported by others²⁸¹. Combined, the results suggest that GDS total scores primarily reflect anxiety or apathy rather than dysphoria. As dysphoria could be reasoned central in the concept of major depression (Figure 6), this could question the validity of the GDS total score, at least in samples where apathy and anxiety are prevalent - as in older adults at risk of AD¹⁵³.

Much fewer studies have addressed the relationship between depression and tau. In general, the literature on CSF biomarkers is not in favor of such a relationship^{256, 257, 270-272}. However, a cross-sectional PET imaging study showed that a higher level of depressive symptoms (measured by the GDS) is related to more tau in the inferior temporal and entorhinal cortex among CU older adults²⁸². In line, CU individuals with an increased cerebral tau load have been reported more likely to have a clinical diagnosis of depression²⁷⁴. Additionally, increased tau deposition, especially in the entorhinal cortex and other temporal structures, has been reported related to several behavioral features, including higher levels of depression, among individuals at increased risk of future AD²⁶⁵.

Concerning neurodegeneration, depression in predominately advanced stages of AD is associated with atrophy in frontotemporal and subcortical brain regions²⁸³⁻²⁸⁷. It has been debated whether these associations arise by an actual effect by LLD, independent from AD-related changes, or if these associations are due to confounding by underlying AD pathology. According to a meta-analysis on the topic, AD is strongly related to cortical atrophy in the brain's parietal, frontal, and temporal areas. In contrast, LLD is mainly associated with atrophy in frontal brain regions. Intriguingly, both AD and LLD were found independently related to hippocampal volume loss²⁸⁴. This finding once more encourages the idea that depression can lower resilience factors against cognitive impairment, and hence lower the threshold for displaying clinically significant symptoms if AD pathology eventually develops.

The relationship between Alzheimer's disease pathology and anxiety

The relationship between anxiety and AD-related pathology is less studied than depression and apathy, but the findings are somewhat more consistent²⁸⁸.

There are both CSF and PET studies that denote anxiety as related to A β pathology in non-demented stages of disease^{247, 257, 259, 277, 278, 280, 289, 290}. Cross-sectional studies have demonstrated anxiety associated with A β deposition in both cortical and subcortical brain regions^{259, 277, 278, 289}. Increased anxiety levels have further been shown associated with increased odds of having elevated A β deposition^{259, 278}. Pointing to an effect by A β pathology, a longitudinal study on CU older adults displayed steeper rates of increased anxiety-concentration cluster-item scores, obtained by the GDS, in individuals with elevated levels of A β at study start²⁸⁰. This finding was recently supported by another study on older adults without dementia²⁹⁰.

The literature on anxiety and its relation to tau pathology or neurodegeneration is still scarce. A large sampled cross-sectional CSF study, covering several stages of disease, indicates that both greater A β and tau pathology relate to greater levels of anxiety²⁴⁷. Opposing a relationship with tau, a longitudinal PET study on anxiety in non-demented individuals could instead not report an association between the presence of tau and the evolution of anxious symptomatology. There is further evidence of an association between anxiety and neurodegeneration in a neurocognitive context from the use of fluoro-deoxyglucose PET²⁹⁰, CSF analyses²⁵⁷, and structural MRI²⁹¹.

The relationship between white matter lesions and certain neuropsychiatric symptoms

WML have been demonstrated linked to NPS. Apathy has been consistently related to WML in frontal and subcortical brain regions^{255, 267}. However, it is important to point out that most of these findings rest upon cross-sectional data. A longitudinal study on CU elderly could not display an effect of WML on the development of apathy during five years of follow-up²⁴⁶. Considering large-vessel disease, apathy has been demonstrated to occur in every third patient after major stroke in what is termed “*poststroke apathy*”²⁹².

Reports are mainly in support of a relationship between cerebrovascular disease and depressive symptoms in older adults²⁸³. Some studies support that depression in AD is associated with WML predominately in the basal ganglia, the frontal lobe, and the parietal lobe^{283, 293}. However, most studies are conducted on later stages of disease, and compared to the cross-sectional findings on apathy, the relationship between depression and WML remains somewhat less consistent²⁸³. *Poststroke depression* is reported to be as frequent as poststroke apathy²⁹⁴.

Only few are the reports on the impact of WML on anxiety in neurodegenerative cohorts, and they display somewhat conflicting results^{295, 296}, wherefore firm conclusions cannot be made.

Pharmacological treatment of neuropsychiatric symptoms

Bearing in mind that NPS in AD and other ND are associated with several adverse outcomes, it has been postulated that early identification and treatment of NPS in AD may slow disease progression or mitigate distress. Unfortunately, at present, there is no approved pharmacological treatment for any NPS labeled explicitly for use in AD or other ND¹⁰⁹. However, there are several promising ongoing clinical trials^{8, 109}.

Methylphenidate has recently, in a phase-III placebo-controlled randomized clinical trial, including 200 participants with possible or probable AD, been demonstrated to be safely tolerated and to have a small to medium effect on apathy levels²⁹⁷. These findings further align with previous smaller studies²⁹⁸.

Numerous reports in the literature argue against an effect of antidepressants such as selective serotonin reuptake inhibitors (SSRI) on depression in AD²⁹⁹. Yet there are exceptions. In a small sample-sized randomized placebo-controlled study, SSRIs were demonstrated to significantly improve depressive symptoms among participants with probable AD³⁰⁰. Notably, this study recognized the potential overlap between symptoms of cognitive deterioration and depression (and possibly unintentionally also apathy). The need to separate core depressive symptoms from cognitive deterioration or apathy as far as possible is further stressed by the descriptions of SSRI-induced apathy. Yet, these primarily rest upon case reports and a few retrospective findings³⁰¹⁻³⁰³.

In clinical practice, benzodiazepines are commonly used in short time durations to handle more profound anxiety. However, there is limited evidence for their clinical utility as they are demonstrated to negatively impact cognition, increase the risk of falls or confusion, and other adverse drug reactions³⁰⁴.

Psychometric evaluation of neuropsychiatric symptoms

Rating scales for neuropsychiatric symptoms

Syndromic diagnostic criteria are instruments to identify individuals with a supposed common underlying pathological process, manifesting by a conglomerate of clinical symptoms or signs. However, diagnostic criteria do not serve as strong methods to quantifying disease severity.

Rating scales, however, have the primary aim to quantify (latent) characteristics of individuals that cannot be measured directly, such as the severity of mental experiences or behaviour^{305, 306}. They are most frequently designed to map out the latent constructs as continuums on which the individual can be positioned^{301, 302}. Such tools are widely used and serve as screening instruments, aid in diagnostic considerations, measurements of severity, and means to monitor intervention outcomes³⁰⁷. Accordingly, they influence interpretation and decision-making in both research and clinical settings. Therefore, it is a requirement that rating scales are rigorous measures of the aspects they claim to quantify.

The scientific discipline concerned with the theory and technique of quantifying mental capacities and related processes by measurements, assessments, or tests is referred to as *psychometrics*³⁰⁸. The overall aim of psychometric studies is to establish the extent to which a quantitative conceptualization of the construct (in this case, various NPS) has been operationalized successfully³⁰⁶. There are several psychometric methodologies to be used, such as the traditional *Classical Test Theory* (CTT) and more recent approaches such as Rasch analysis and Item Response Theory^{305, 306, 309, 310}.

Basic concepts of Classical Test Theory

Data quality

Data quality refers to the extent to which a rating scale can be administered successfully among responders in the sample of interest. Percentage of missing item responses and percentage of the sample for whom total scores could be calculated, are indicators of data quality^{306, 311}.

Targeting

Targeting concerns the match between the distribution of distress or disability in the sample and the range of distress or disability measured by the scale. This can be addressed by evaluating *score distributions*, *skewness statistics*, as well as the level of *floor and ceiling effects*. Floor/ceiling effects up to 20% are generally accepted³⁰⁶.

Scaling assumptions

Scaling assumptions tests whether it is legitimate to sum individual item scores to generate a single scale total score. To ascertain the appropriateness to sum up items into a total score, a set of criteria are to be fulfilled³⁰⁶. First, the individual items should measure the same point on the total scale of distress or disability and have a similar variance. Second, the items should measure the same underlying construct (in this case, NPS). These two criteria can be explored by measures of internal consistency (outlined below) and corrected item-total correlations^{306, 311}. In the latter, each individual item ought to correlate with the summed total score above a recommended criterion between 0.4-0.8³⁰⁶. Another way to explore if the items represent a common underlying construct is by data reduction techniques (as *Principal Component Analysis* [PCA]) that display scale dimensionality^{305, 312}.

Dimensionality

To legitimately sum individual items into a total score, all items need to reflect a single common underlying dimension (by some called component, factor, construct, or variable)^{305, 312}. If a scale is made up of several dimensions (e.g., both depression and anxiety), the computation of separate total scores could be questioned. The number of dimensions and their sizes can be demonstrated using PCA, a data reduction technique that analyzes item correlations to find the “components” of the items that convey maximum variation and minimal error in the data set³¹³.

Reliability

The degree to which scale scores are precise and free from measurement error defines the term reliability. Internal consistency, reproducibility, and responsiveness are three important concepts surrounding reliability³⁰⁶.

Internal consistency is a combined measure of the correlations between the scale items. Too low internal consistency indicates that the items do not measure the same underlying construct. If the consistency is too high, some items might instead be redundant. The internal consistency can be statistically determined by Cronbach's coefficient alpha, which calculates the summed error associated with scores from intercorrelations among the items. Its value should be above 0.70 and preferably even above 0.80³⁰⁶.

Reproducibility is determined by the extent to which results obtained from a rating scale can be achieved once more if the assessment is repeated. Suppose the assessment is re-administered to an individual with stable characteristics, and the assessment yields a similar result. In that case, the combined results would support the assessment to have a high *test-retest reliability*^{305, 306}.

Responsiveness

Responsiveness is the ability to detect change accurately when it has occurred. A basic and clinically meaningful psychometric method for responsiveness is the calculation of *Standard Error of Measurement* (SEM). It is defined as an estimate of the variation around a "true" score for an individual when repeated measures are taken. From samples, it can be generated by the standard deviation multiplied by the square root of 1 minus the internal consistency. SEM allows calculating confidence intervals likely to contain the "true" score of an individual with a certain degree of confidence³⁰⁶.

Validity

When a scale measures what it claims to measure, validity is reached^{305, 314}. There are several subtypes of validity.

Construct validity refers to whether the scale relates to other measures in a pre-hypothesized way. Two important subtypes of construct validity are *convergent* and *discriminant validity*. Convergent validity refers to the degree to which two measures of a construct, that theoretically should be related, are in fact related. In contrast, discriminative validity tests whether concepts or measurements that are supposed to be unrelated, in fact are unrelated. For example, apathy assessments should theoretically be closely correlated to ratings of depressive severity, but not the level of memory impairment measured by a cognitive test³¹⁴.

Criterion validity is the extent to which a rating scale relates to the theoretical representation of the construct as measured by a golden standard³¹⁴. This is often a

difficult task in the field of psychiatry since well-functioning golden standards are often missing³¹⁴. For instance, a self-rated rating scale of depression severity could be compared to individual interviews by more “objective” clinicians. However, also clinician interviews have been reported problematic³¹⁵.

Content validity in psychometrics is defined by the extent to which a measure represents the various facets of the construct of interest³¹⁴. For instance, the construct “depression” encompasses not only depressed mood it is also defined by pessimistic thoughts and suicidal ideation, which then ought to be represented by the scale items. This type of validity predominately rests upon subject matter expert opinions.

Face validity concerns if items in the rating scale appear suitable in the light of its aim and the nature of the construct it purports to measure³¹⁴. Decisions on this type of validity are also evaluated by subject matter experts.

Challenges in rater source selection

Besides the internal features of rating scales, it is also important to consider the utility of different rater sources when assessing NPS. Depending on the clinical stage of AD, rater sources can provide different challenges, ultimately affecting the reliability of the assessment.

Self-ratings have the potential to register both the internal psychological experiences as well as related external behavior, whereas informant-ratings predominantly reflect the latter.

As AD progresses, the reliability of self-ratings could be assumed to drop due to cognitive difficulties such as comprehension deficits or anosognosia (lack of insight)³¹⁶⁻³¹⁹. In support, a study on the Apathy Evaluation Scale (AES) demonstrated that CU individuals tend to report somewhat greater apathy levels over time than their informants or clinicians. MCI participants, on the other hand, seem to under-report the apathy severity compared to informants or clinicians³²⁰. This argues for the use of informant or clinician-rated assessments in clinical stages of disease.

Informant-ratings, however, are well-known to be biased by rising levels of caregiver burden, resulting in higher ratings of the patients’ distress or disability^{321, 322}. Hence, in situations where the cognitive functions are compromised, and the caregivers are overburdened, clinician-ratings might serve as a more suitable method. Clinicians, however, often only see their patients during short times. Therefore, they might fail to properly register NPS that fluctuate, or fail to detect more subtle changes in mood or behavior that could unveil during observations with more extended time duration.

Altogether, the various rater-sources display distinct limitations that turn critical in different stages of disease.

Rationale and aims

General aim

The general aim of this thesis has been to examine the relationships between certain NPS (apathy, anxiety, and depression), cognitive impairment and core AD-related pathologies in non-demented individuals.

The thesis has further aimed to provide a psychometrically favorable rating scale for apathy in Swedish.

Specific rationale and aims

Paper I

A rating scale for the level of apathy in early AD was lacking in Swedish, potentially halting clinical and research efforts. Moreover, few previous studies had addressed basic psychometric properties of the AES according to CTT principles, or assessed dimensionality by methods taking into account the ordinal nature of the data generated by the individual items.

Hence, paper I aimed to translate and psychometrically evaluate a Swedish version of the AES. This by comparing its properties with findings from the original English version, as well as by utilizing CTT principles and more modern PCA methods.

Paper II

Several key AD hallmarks had rarely in unison been explored in relation to NPS in early stages of disease, using one common sample.

Paper II, therefore, aimed to study the cross-sectional relationships between certain neuropsychiatric symptoms (apathy, anxiety, and depression) and A β deposition, cerebral atrophy, WML, and future cognitive decline in a non-demented sample covering both CU and MCI subjects.

Paper III

It remained to be demonstrated whether MBI precedes or follows cognitive deficits in biomarker confirmed preclinical AD, and whether MBI is associated with tau pathology in this early phase.

Accordingly, the aim of paper III was to explore cross-sectional associations between MBI and biomarkers of tau pathology in preclinical stages of AD and further to compare associations with tau for MBI and episodic memory impairment.

Paper IV

Prior studies had rarely investigated the effects of both AD-related pathology and cognition on the development of NPS²¹¹. Therefore, the exact temporal and causal relationships between neuropathology, cognition, and NPS in AD have remained unclear.

In paper IV, an attempt was made to disentangle these relationships. The specific aim was to study how biomarkers of AD pathology, WML, or cognitive deficits potentially drive the development of apathy, anxiety, and depressive symptoms in CU older adults. A second aim was to explore if cognitive change mediates the effect of different brain pathologies on longitudinal NPS.

Methods

All data in the thesis originate from the prospective and longitudinal Swedish BIOFINDER (Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably) Study (www.biofinder.se), launched in 2008. The study was initiated with the ambition to discover core pathological mechanisms in AD and other ND. The study includes large-sampled cohorts of CU individuals, as well as patients with MCI, dementia, or parkinsonian disorders (Figure 8). The participants have been thoroughly and repeatedly examined (each year or biennially, depending on cohort and type of examination) with clinical assessments, cognitive tests, assessment scales (e.g., covering NPS), analyses of AD-related biomarkers in CSF and plasma, as well as neuroimaging with MRI and amyloid-PET.

In 2017, the Swedish BIOFINDER study (BF-I) was complemented by the updated Swedish BIOFINDER 2 Study (BF-II), including tau-PET, as well as optimized MRI methods and clinical assessments.

Paper I, II, and IV are based on data from BF-I, whereas data in paper III is derived from BF-II.

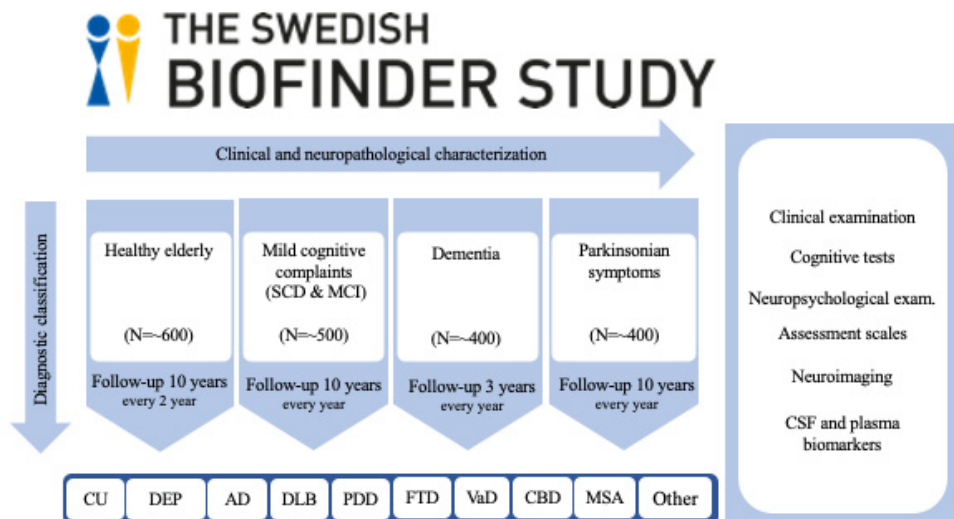


Figure 8. Schematic illustration of the Swedish BIOFINDER I Study. Used and modified by courtesy of Oskar Hansson

Study populations

Cognitively unimpaired in the BIOFINDER-I study

In BF-I, the cohort comprising CU controls was recruited from the population-based Malmö Diet Cancer Study³²³. Subjects were eligible for inclusion if they i) were \geq 60 years old, ii) had Mini Mental State Examination (MMSE) 28–30 at the screening visit, iii) did not need a Swedish interpreter, iv) had absence of cognitive symptoms, and v) did not fulfill criteria of MCI or dementia. Exclusion criteria were a) presence of significant neurological or psychiatric disease, e.g., PD or ongoing severe major depression, b) significant unstable systemic illness or organ failure, c) refusing lumbar puncture or MRI, and d) significant alcohol or substance misuse. The participants were re-examined biennially.

Mild Cognitive Impairment in the BIOFINDER-I study

Participants in the cohort of patients with MCI, or subjective cognitive deficits (SCD), were recruited consecutively at three memory clinics (in Malmö, Lund and Ängelholm) in the southern part of Sweden. They were included if they i) were referred to the memory clinic due to cognitive symptoms experienced by the patient and/or an informant, ii) did not fulfill criteria for dementia, iii) had MMSE score between 24–30, iv) had an age between 60–80 years old, and v) did not need a Swedish interpreter. Exclusion criteria were a) cognitive impairment that with certainty could be explained by another condition than prodromal dementia, b) significant unstable systemic illness or organ failure, c) refusing lumbar puncture or neuropsychological examination, and d) ongoing alcohol or substance misuse.

For exclusion (both in the CU and MCI BF-I cohort), dementia was defined by the DSM-IV-TR criteria¹⁰⁷. The differentiation between SCD and MCI was based on consensus MCI criteria suggested by Petersen¹⁰⁴ and operationalized by a neuropsychological test battery evaluated by a senior neuropsychologist. Subjects with no measurable cognitive deficits were categorized as having SCD and those with objective cognitive impairment as having MCI⁹³. Using the syndromal staging system in the NIA-AA research framework⁸³, SCD participants were regarded as being CU.

The MCI participants were examined by cognitive tests and assessment scales (not the AES) once a year, while CSF and blood sampling and imaging were performed every second year.

Parkinsonian disorders in the BIOFINDER-I study

The participants in the parkinsonian cohort in BF-I were recruited at the Neurology clinic at Skåne University Hospital in Lund, Sweden. Participants were included and followed repeatedly if they fulfilled diagnostic criteria of PD, PDD, or DLB³²⁴⁻

³²⁶, including those with only early parkinsonian symptoms. Exclusion criteria were significant unstable systemic illness or current significant alcohol or substance abuse.

Clinical and cognitive assessments were retaken every year, and clinical, cognitive, neurological, and psychiatric assessments, as well as biofluid sampling and MRI, were repeated biennially.

Cognitively unimpaired in the BIOFINDER-II study

The CU sample used in paper III was derived from three of the cohorts in BF-II and comprised participants representing neurologically and cognitively healthy controls at different age spans (cohort A & B) or participants categorized as having SCD (derived from cohort C).

The inclusion criteria for cohorts A and B were i) age between 40-65 years (cohort A) or age between 66-100 years (cohort B); ii) absence of cognitive symptoms as evaluated by a physician specialized in cognitive disorders; iii) MMSE score between 27-30 (cohort A) or between 26-30 (cohort B); iv) the subject did not fulfill the criteria for mild or major NCD (MCI or dementia) according to DSM-5³²⁷; and v) fluency in the Swedish language.

Cohort C, from which the SCD participants derived, included subjects with either SCD or MCI. Inclusion criteria were: i) age 40-100 years; ii) referred to one of the memory clinics due to cognitive symptoms; iii) a MMSE score between 24-30; iv) no fulfillment of criteria for major NCD according to DSM-5³²⁷, v) fluency in Swedish.

A slightly different methodology for separation between SCD and MCI was used in BF-II compared to BF-I. In BF-II, the subjects in cohort C that performed worse than -1.5 SD in any cognitive domain, using a neuropsychological cognitive test battery, and according to age and education stratified test norms, were classified as having MCI⁹². Subjects not classified as MCI were considered to have SCD. As in BF-I, subjects with SCD were regarded as being CU⁸³.

Assessments

Rating scales for neuropsychiatric symptoms

Apathy Evaluation Scale

Initially developed by Marin et al. ³²⁸, AES is today one of the most widespread and well-studied rating scales for assessing apathy severity³²⁹. The assessment is constructed to cover the affective, behavioral, and cognitive aspects of apathy during the prior 4-week period. It is intended for use among older adults aged above

55 and has been evaluated in a variety of diseases such as AD, PD, cerebrovascular disorders, major depression, schizophrenia, as well as in older healthy subjects^{329, 330}. There are three different rater source versions, including a clinician-administered semi-structured interview version (AES-C), a self-rated version (AES-S), and an informant-rated version (AES-I) for completion by proxies. In this thesis, only AES-S and AES-I were used (AES-S is demonstrated in the appendix). The different versions cover the same 18 items rated at a four-point Likert scale ("Not at all," "Slightly," "Somewhat," and "A lot"; scored 1-4, respectively). Following reversed scoring for three items, item scores are summed into a total score ranging between 18-72 (higher scores indicating more apathy).

The AES has in several studies been shown to have a factor structure with three dimensions, where most items have loaded on the "apathy" component, which also has accounted for most of the variance^{328, 331}. Hence, the rating scale has most often been handled as unidimensional in clinical practice and research studies. Arguing for good internal reliability, the internal consistency is reported to range between 0.86-0.94³²⁹. Favorable test-retest reliability is also demonstrated³²⁸. Moreover, the AES has been reported to have a fair to moderate convergent and discriminate validity, indicating a good construct validity³²⁹.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a well-established rating scale consisting of 14 items. Seven items relate to depression severity (HADS-D) and seven to anxiety severity (HADS-A). Each item is scored 0-3 points. Total scores range between 0 to 21. The higher the score, the worse symptomatology^{332, 333}. The rating tool has demonstrated acceptable and unidimensional psychometric properties in samples of older adults³³⁴.

Mild Behavioral Impairment – Checklist

The MBI Checklist (MBI-C) was developed to capture MBI in accordance with the ISTAART-AA criteria for MBI^{10, 335}. The MBI-C covers 34 items, representing five domains: i) decreased drive and motivation (apathy, comprising 6 items, range 0-18 points), ii) affective dysregulation (mood and anxiety symptoms, comprising 6 items, range 0-18 points), iii) impulse dyscontrol (agitation, impulsivity, and abnormal reward salience, comprising 12 items, range 0-36 points), iv) social inappropriateness (impaired social cognition, comprising 5 items, range 0-15 points), and v) abnormal perception and thought content (psychotic symptoms, comprising 5 items, range 0-15 points). Each item question is answered with "No" (0 points) or "Yes" depending on if the actual symptoms have persisted for at least 6 months (continuously or intermittently) and represent a clear alteration from the rated person's normal behavior. Items answered "Yes" are followed by a severity rating of either 1 point = mild, 2 points = moderate, or 3 points = severe. A MBI-C total score (range 0-102 points) is calculated by summing the scores of each item.

Total scores for each domain can also be generated. Importantly, the MBI-C instructs that the symptoms to be measured shall have emerged late in life and persisted for at least 6 months. Score distributions, factor structure, sensitivity, specificity, and the diagnostic utility of MBI-C have been validated in cohorts of SCD³³⁶, MCI³³⁷, and population-based samples of CU³³⁸. A Swedish version of MBI-C has been developed in the context of this thesis and is available in the appendix and at www.MBItest.org³³⁵.

Cognitive tests

Mini-Mental State Examination

MMSE is undisputedly one of the most popular and widely used tests to quantify cognitive functioning³³⁹. The test was introduced in 1975 by Folstein³⁴⁰, and it consists of ten items assessing function in different cognitive domains. The scores obtained from each item are summed into a total score ranging between 0-30, representing the global cognitive functioning. Lower scores indicate worse global cognition³⁴⁰. The test has demonstrated good sensitivity and specificity for the detection of dementia³³⁹. However, the detection of cognitive change over time and its predictive capacity of future dementia in early stages of disease is shown outperformed by other more specific cognitive tests³⁴¹.

The Modified Preclinical Alzheimer Cognitive Composite

The Preclinical Alzheimer Cognitive Composite (PACC5) was developed as a sensitive tool to detect cognitive change in preclinical stages of AD³⁴². It is a composite of several cognitive tests. The PACC5 was later slightly modified into mPACC5 by replacing a logical memory test and the Free and Cued Selective Reminding test by The Delayed Word Recall Test (ADAS-DR) from The Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog)³⁴³. Furthermore, in the mPACC5 used in paper IV, the original executive test was replaced by the color-form task in A Quick Test of cognitive speed (AQT-CF)^{92, 344}.

The mPACC5 was computed as the average of five z-scores (calculated by [the observed test score minus the sample mean] divided by the standard deviation), given by tests of global cognition (MMSE), episodic memory (ADAS-DR, counted twice to preserve the weight on memory from the original PACC), verbal fluency (Animal Fluency Test), and executive functioning (AQT-CF)³⁴².

A Quick Test of cognitive speed - the color-form task

In the AQT-CF task, the participant quickly names the color and form of 40 objects (square, circle, triangle, and line) with different colors (red, yellow, blue, or black). The score constitutes the number of seconds it takes to complete the task. The test was originally developed as an alternative to the executive Stroop test that could be administered to illiterate participants or participants with a lower level of

education^{344, 345}. The test has shown favorable properties in detecting early treatment responses in AD³⁴⁶.

Alzheimer Disease Assessment Scale-Delayed Word Recall

ADAS-DR is a cognitive test to assess the level of episodic memory deficit. The subject being assessed is given three trials to learn a list of ten high-frequency, high-imagery nouns printed in block letters on white cards. After a few minutes of distraction (often by other cognitive tasks), the subject is asked, in one trial, to recall the ten words previously presented. The number of words not recalled is counted (maximum 10 points), and the higher the score, the greater the subject's memory deficit³⁴⁷. Tests of delayed recall have been shown sensitive and specific indicators of AD³⁴⁸.

Measures of in vivo neuropathology

Fluid-based biomarkers

CSF and blood samples were collected and handled according to structured protocols^{349, 350}. The immunoassays used to quantify the level of the biomarkers vary between the papers.

In paper III, CSF A β 42 and A β 40 were determined using Meso Scale Discovery immunoassays (MSD; Rockville, MD, USA)³⁵¹, whereas P-tau181 was obtained using Innostest[®] immunoassay (Fujirebio; Gent, Belgium). In paper III, CSF A β 42 and A β 40 were combined into a CSF A β 42/40 ratio, with high specificity for AD-related amyloidopathy⁸⁵. A β -positivity was defined by the A β 42/A β 40 cut-off < 0.752 (obtained using gaussian mixture modeling)³⁵² and used for sample selection. CSF P-tau181 was used as a continuous measure reflecting cerebral tau load.

In paper IV, levels of CSF A β 42, A β 40 and NfL were measured on an Elecsys platform (Roche Diagnostics International Ltd.)^{350, 353}. Also in this study, CSF A β 42 and A β 40 were combined into a CSF A β 42/40 ratio. In this paper, the CSF A β 42/A β 40 ratio was used as a proxy for the level of cerebral A β deposition. CSF NfL was used as a marker for cortical and subcortical axonal degeneration³⁵⁴. Plasma P-tau217, representing the level of tau tangle pathology, was analyzed using an immunoassay on a Mesoscale Discovery platform developed by Lilly Research Laboratories³⁵⁰.

Positron emission tomography

To quantify the cerebral load of A β plaques in paper II, ¹⁸F-flutemetamol-PET/Computed tomography was conducted. PET sum images from 90 to 110 min post-injection of the tracer were generated for the average uptake. The NeuroMarQ

software (GE Healthcare) was used to analyze the images. A volume template was applied for nine bilateral cortical regions of interest (ROI) (prefrontal, parietal, lateral temporal, medial temporal, sensorimotor, occipital, anterior cingulate, and posterior cingulate/precuneus), later combined in a global cortical composite signal. Most analyses encompassed continuous PET A β measures; however, a few analyses used a dichotomization of the measure into A β -negatives or A β -positives, based on a formerly defined cut-off (>1.42 SUVR)³⁵¹.

In paper III, cerebral tau pathology was quantified using [¹⁸F]RO948-PET. Sum images were generated 70-90-minutes post-injection of the tracer. Standardized uptake value ratio images were created using the inferior cerebellar cortex as reference region³⁵⁵. ROIs were based on the parcellation of the T1-weighted MRI using FreeSurfer v6.0. In order to capture brain areas affected by tau deposition over the temporal course of AD, three composite ROIs were created according to the Braak tau pathology staging scheme⁷¹. These include region I-II (the entorhinal cortex and hippocampus), region III-IV (parahippocampal cortices, fusiform cortices, amygdala, as well as the inferior and the middle temporal cortices), and region V-VI (widespread neocortical areas)⁷⁰. To explore regional associations, also voxel-wise based multiple regression modeling was performed (outlined in the statistical section).

Magnetic resonance imaging

In paper II, measures of the level of cerebral atrophy were attained by high-resolution MRI T1-weighted MP-RAGE sequences. Cortical thickness (the distance from the gray/white matter boundary to the corresponding pial surface) was used as a proxy for the level of cortical atrophy. Cortical reconstruction using the software FreeSurfer v5.3 permitted parcellation into cortical ROIs according to the Desikan-Killiany atlas^{356, 357}. As a proxy for temporal atrophy, a composite thickness measure that previously has been shown sensitive to atrophy in AD (“AD-signature cortex”) was used³⁵⁸, and included the entorhinal, inferior temporal, middle temporal, and fusiform cortices. Supplementary to the ROI-based cortical atrophy analyses, “whole-brain” cortical vertex-based regression analyses were also performed (outlined in the statistic section).

Subcortical volumes were used as a proxy for the level of subcortical atrophy in paper II. Contrary to the cortical regions, registration, and segmentation of subcortical regional volumes (the bilateral amygdala, hippocampus, nucleus accumbens, caudate nucleus, putamen, pallidum, and thalamus) were performed using the software FIRST^{359, 360}. This software was selected instead of FreeSurfer when the subcortical structures were analyzed; this given its superior segmentation of these structures upon visual inspection.

Measures of global WML volumes in paper II-IV were acquired by an automated data segmentation method on T2-weighted MRI FLAIR sequences, using the lesion

prediction algorithm in the LST toolbox for SPM³⁶¹, providing a volume variable of ratio scale. Additionally in paper II, a visual rating of FLAIR images was performed by a radiologist according to the Age-Related White Matter Change (ARWMC) scale³⁶², generating an ordinal measurement variable. Besides assessing the global burden of WML, the ARWMC scale also assesses five bilateral regional WML volumes (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial).

Statistical analyses

Principal component analyses

To examine the scale dimensionality (paper I) PCAs were used. In short, a PCA is a data reduction technique that calculates the “best” linear combinations of the original items in order to explain the maximum variance among the scale item data points. This is achieved by rotating the “line of best fit” among data points in a multidimensional covariance matrix (as many dimensions as items)³⁶³. Different rotation methods include orthogonal (encompassing the varimax rotation as used in paper I) or oblique rotation. These are chosen depending on if the components are allowed to correlate or not³⁶⁴. PCAs also provide us with eigenvalues. These are estimations of the “weight” or “importance” of the extracted components (dimensions). Eigenvalue >1 is a coarse criterion for a component to explain enough variance in the item data set to be statistically meaningful to extract. The criterion is often criticized for being too liberal in identifying components³¹². Moreover, traditional PCAs are most often based on a matrix of inter-item Pearson correlations, which assumes at least interval-level variables. Hence, ordinal item-level data as provided by the AES might not be suitable for these traditional methods. Hence, a more modern approach using PCA based on a matrix of polychoric correlations was also applied and combined with a less arbitrary method to determine the number of relevant components by the use of parallel analysis^{365, 366}.

Multiple linear regression analyses

The goal of multiple linear regression is to statistically model, estimate or predict the linear relationship between a set of independent (explanatory) variables and a dependent (response) variable³⁶⁷⁻³⁶⁹.

In paper II, cross-sectional associations between NPS and biomarkers of neuropathology were explored by such regression models. These models can schematically be depicted as:

$$\text{NPS} \sim \text{biomarker} + \text{covariates} + \varepsilon$$

Accordingly, each of the studied NPS was entered as a continuous dependent variable to be explained. The various biomarkers of neuropathology, respectively, were entered as continuous independent explanatory variables. To control the associations for age, sex, years in education, and global cognition (MMSE), these variables were entered as covariates. The symbol ε denotes random error. Underpinning assumptions for these regression analyses were assessed by evaluating normality and homoscedasticity of residuals with probability plots and plots of residuals versus fitted values³⁶⁹.

These primary analyses in paper II were further extended to encompass vertex-based regression analyses for NPS and cortical atrophy. These analyses had the aim to investigate associations using a less hypothesis-driven analysis (not restricted to prespecified ROIs) and allowed visualization of focal structural changes throughout the entire cerebral cortex. Accordingly, FreeSurfer software was used to create a general linear model analysis of the cortical thickness at each vertex of the cortical surface³⁷⁷. The dependent variable was cortical grey matter thickness difference, and here also, the nuisance variables (being controlled for) were age, sex, education, and MMSE.

In the main linear regression analyses in paper III, MBI-C or ADAS-DR, respectively, was used as the independent variable, while tau-PET values in the various ROIs (representing the different Braak stages) or CSF P-tau181 were entered in separate models as the dependent variable to be predicted. These models were also adjusted for age, sex, education, and WML volume.

In paper III, a secondary analysis using voxel-wise multiple regression modeling was also performed³⁷⁰. This whole-brain analysis aimed at demonstrating and visualizing the associations between the global burden of NPS (measured by MBI-C) and the intensity of tracer uptake using tau-PET at each voxel in the acquired images. The models also included age, sex, education, and WML volume as covariates.

Linear mixed effect models

In papers II and IV, longitudinal data were used to investigate how either cognition (paper II) or NPS (paper IV) develop over time under the influence of NPS (paper II), cognition (paper IV), or neuropathology (paper II and IV), respectively. As this involves multiple responses (data points) from each research participant, ordinary multiple linear regression models could not be used. Instead, Linear Mixed Effect (LME) models were performed based on multiple linear regression modeling, including random slopes and intercepts (schematically depicted below)³⁶⁹.

Longitudinal cognition ~ baseline NPS*time + covariates +(1+time / ID) + ε

or

Longitudinal NPS ~ baseline cognition*time + covariates +(1+time / ID) + ε

In paper II, continuous measures of baseline NPS or Aβ status (dichotomous variable) were entered as independent variables to explore their effect over time on the future development of global cognition (dependent variable, measured by MMSE). The models were controlled for age, sex, and level of education. As individuals tend to start out with different levels of cognitive function or have different slopes in their cognitive decline (change over time), these variables were entered as random intercepts or slopes ([1+time / ID]). To address the effect by NPS or Aβ status over time, interaction variables between the independent variable and time were entered in the models (indicated by the asterisk in the formula). In a set of models, we further investigated the interacting effect of NPS and Aβ status using three-way interaction variables with time (NPS*Aβ*time).

In paper IV, somewhat similar LME models were applied. Baseline levels of neuropathology or cognitive test performance, as well as cognitive change, were entered as independent variables interacting with time. Longitudinal measures of NPS were entered as independent dependent variables, respectively. As in paper II, these models included age, sex, education as covariates and random intercepts and slopes.

Also here, underpinning assumptions were assessed by evaluating normality and homoscedasticity of residuals with probability plots and plots of residuals versus fitted values³⁶⁹.

Mediation analyses

In paper IV, causal mediation analyses were also performed³⁷¹. These were based on linear regression models with the aim to explore if cognitive impairment mediates the statistical effect of AD-related pathologies on the development of NPS. A bootstrap procedure (n=1000 iterations) calculated 95% CI for the mediated effects.

Imputation of missing data

Missing data occur in almost all research and can impact statistical power and generate biased results. Missing data can, in some instances, be replaced by imputation of new values. There are several methodological approaches for imputation³⁷². In paper III, additionally to analyzing raw data with available MBI-C item responses, imputation of missing item responses was conducted. This was done using a single imputation procedure using the “aregImpute” function in the Hmisc package in the statistical software R.

Corrections for multiple comparisons

When multiple statistical tests are performed, the likelihood of having some false-positive results (type-I error) increases with the number of tests³⁷³. To account for this problem, there are several statistical approaches, such as Bonferroni correction or False Discovery Rate (FDR) correction, which adjusts the p-values according to the probability that one or more of the rejected hypotheses is true or the expected number of false rejections among the rejected hypotheses, respectively. However, too strict corrections of the p-values increase the risk of dismissing a significant result as false when it is significant (type-II error). FDR correction is considered less conservative than the Bonferroni method when greater numbers of tests are performed³⁷³. The Bonferroni method was used in paper IV, whereas FDR correction for multiple comparisons was carried out in paper II.

Ethical considerations

The studies were approved by the local ethical review board and was conducted according to the Declaration of Helsinki. All participants gave their written consent. Approvals for PET imaging were obtained from the Swedish Medicines and Products Agency, and the local Radiation Safety Committee at Skåne University Hospital, Sweden.

Main results and conclusions

Paper I

Sample

226 CU controls, 201 patients with SCD or MCI, and 88 patients with parkinsonian symptoms were recruited from the BF-I cohorts. 461 complete AES-S (self) ratings and 403 complete AES-I (informant) ratings could be extracted from these participants. Some individuals had missing AES data due to incomplete neuropsychological data (n=4), lack of a close relative to complete the AES-I forms (n=87), or no consent to fill out specifically the AES (n=4).

Main results

Concerning data quality, total scores could be calculated in 89.5-95.5% of the total sample, with the lower percentage representing individuals with parkinsonian symptoms and the higher percentage CU individuals. Item-level completeness ranged between 96.8 and 100%, with lower values representing items 6 or 11.

In support of achieved scaling assumptions (to legitimate sum items scores into a total score), AES-S and AES-I item mean scores in the total sample ranged from 1.6-2.3 and 1.8-2.2, respectively. Item SD ranged from 0.8-1.1 for both forms. Corrected item-total correlation in the total sample was >0.5 , except for item 6, which once more represented the item with the worst performance (corrected item-total correlation 0.37). Further supporting summation of items into a total score, the polychoric-based PCA with parallel analysis yielded good evidence for both AES versions to be unidimensional. However, the traditional PCA analyses suggested both AES versions to have a two-dimensional structure, but with the primary component explaining 61.2-62.8% of the variance in the data set and the secondary component (mainly consisting of item 15 and the double negatively worded item 6, 10 and 11) explaining only 6.0-6.5%. Studies of the English original AES versions using traditional PCA^{328,331}, have reported 2- or 3-dimensions, of which the smaller components mainly have represented items 6, 10, 11, or 15.

Targeting analyses (concerning whether the sample's level of apathy matches the range of apathy represented by the scale) showed mean total scores (34.2 and 36.6 for AES-S and AES-I, respectively) somewhat below the scale mid-point (54

points). However, the mid-point was located within 1 SD of the observed mean scores. Floor and ceiling effects were found low (floor effect of ~3%, ceiling effect close to 0%).

The internal reliability was shown favorable, with Cronbach's alpha values of 0.95, corroborating with those originally reported by Marin et al.³²⁸. SEM was calculated to 2.7-2.9, and the mean inter-item correlations for AES-S and AES-I were 0.52 and 0.53, respectively. This provides evidence that AES-S and AES-I meet basic premises for detecting group differences and changes over time.

Exploring convergent and discriminative validity, the correlation coefficient between AES-S and AES-I for the total sample was 0.74. AES-S and HADS-D had a correlation coefficient of 0.48 and AES-S and HADS-A 0.35. Corresponding coefficients for the AES-I were 0.35 and 0.21. These findings also are chiefly in line with those reported by Marin et al.³²⁸.

Conclusion

The study provides initial support that the Swedish AES performs similarly to the English original and exhibits acceptable psychometric properties according to CTT, including supported one-dimensionality, and may be adopted for use in clinical and research settings.

Comments

The study in paper I is the first on AES to consider the ordinal nature of item-level data by conducting polychoric-based PCA analyses for scale dimensionality. These analyses provided novel and uniform evidence for AES reflecting a single psychological variable (apathy), and accordingly that item scores can legitimately be summed to a total score. However, in alignment with previous findings³³¹, the traditional PCA based on Pearson correlations suggested a second component for both versions, consisting mainly of item 15 and the double negatively worded items. These were also the items in the third component reported in the original study by Marin et al.³²⁸. In paper I, the percentage of data completeness for these items was low, as well as the corrected item-total correlations for item 6. Collectively these findings probably reflect the drawback of using two grammatical negations in the same sentence (item 6, 10, and 11) and the theoretical difficulty to value one's own level of understanding of one's problems (item 15).

The study design in paper I did not allow for assessment of test-retest reliability, thorough analyses of responsiveness, or to assess and evaluate the AES-C. This constitutes limitations, together with the inability to have a clinician diagnose the presence or absence of apathy to gain a diagnostic golden standard for analyses of criterion validity, sensitivity, or specificity. Moreover, only a fraction of the participants had a diagnosis of dementia (and these were restricted to individuals with parkinsonian symptoms), and none had yet an established diagnosis of AD.

Paper II

Sample

The study sample in paper II comprised 104 CU individuals (61 CU controls and 43 patients with SCD) and 53 patients with MCI from BF-I.

Main results

Greater global levels of A β deposition in the brain were cross-sectionally associated with higher levels of informant-rated apathy (AES-I) and self-rated anxiety (HADS-A). A β deposition was associated neither with self-rated apathy (AES-I) nor self-rated depressive symptoms (HADS-D).

According to vertex-based morphometry analyses, greater AES-I scores were also cross-sectionally associated with reduced cortical grey matter thickness (atrophy) (Figure 9, panel A). These findings were mainly located to the bilateral temporal lobe and insula, as well as a left-sided more frontal cluster. AES-S scores were only associated with small areas of the temporal cortex in these analyses (Figure 9, panel B). In the ROI-based analysis, a thinner AD-signature cortex (including temporal structures) was also associated with AES-I, but not AES-S. There were no associations between cortical atrophy measures and HADS-A or HADS-D. Increased AES-S and AES-I scores were further associated with smaller volumes of hippocampus, the nucleus accumbens, and some other subcortical structures. Additionally, apathy measures were associated with measures of WML, and so most strongly in the frontal brain regions.

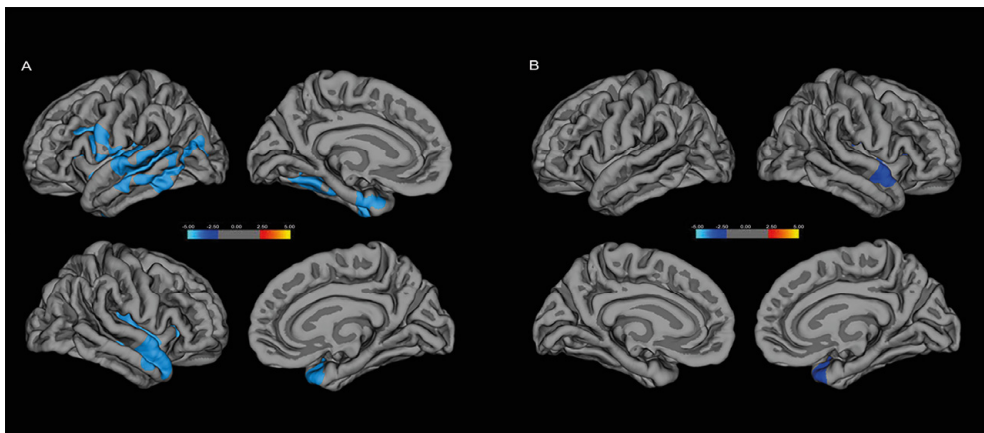


Figure 9. Vertex-based associations between apathy and grey matter thickness.

Vertex-based associations, corrected for age, sex, education, and MMSE, between apathy and cortical grey matter thickness according to grey matter intensity at the significance level $P < 0.05$ ($n = 157$). Panel A shows associations with informant-rated apathy (AES-I). Panel B shows associations with self-rated apathy (AES-S).

In the longitudinal LME models, higher baseline AES-I or HADS-A scores, interacting with time, significantly predicted scores on MMSE (global cognition) over time (Figure 10, panel B & C). However, the effect was mild and found significant only at the 4-year follow-up. Intriguingly, HADS-A scores were found to interact with levels of A β over time on cognitive functioning (Figure 10, panel D). However, this effect was also only mild.

Conclusion

Apathy and anxiety, but not depressive symptoms, are associated with several key hallmarks of AD, such as A β deposition, frontotemporal cortical or subcortical atrophy, or cognitive decline. The associations with A β deposition and future cognitive decline among these non-demented individuals further position these symptoms as early manifestations of the disease.

Comments

The demonstrated significant associations between A β and apathy, or anxiety, corroborate the main previous literature on early stages of disease^{247, 251-255, 257, 259, 277, 278, 280, 289, 290}. However, contrary to these two specific NPS, depressive symptoms were not found related to any key hallmarks of AD. This adds to the ongoing yet inconclusive debate surrounding the role of depression in AD.

Apathy has predominantly been reported related to atrophies in frontal and subcortical brain structures^{155, 266, 267}. However, some reports on early stages of disease have instead demonstrated associations with atrophy in temporal regions²⁶⁸. In this paper, we reported apathy related to frontal, temporal, and subcortical atrophy in a sample encompassing both CU and MCI. One possibility is that the temporal lobes are involved early, whereas atrophy in the frontal and subcortical structures contributes later, explaining the variability between the findings.

Our finding that apathy and anxiety are associated with future cognitive decline aligns with the previous literature and strengthens the indicated clinical usefulness of early recognition of these symptoms when assessing risk of cognitive decline^{216, 217, 223-225, 233-238}.

As in all studies, there are of course limitations. First, most results (not those on cognitive decline) rest upon cross-sectional data; hence the direction of these associations cannot be displayed. Second, most subjects had low anxiety or depression severity, halting the generalizability towards those with only mild psychiatric illness. Third, there were some missing longitudinal MMSE data. However, LME models are known robust towards missing follow-up data. Fourth, a missing data analysis pointed to a slight survival bias, favoring younger cases. Women also had slightly more missing data, especially so for AES-I. This might be

due to their higher likelihood of being a widow, with a subsequent “lack of a close relative” to fill out the forms.

A strength of the study was that confounding between the investigated NPS were analyzed. However, no significant such effect was found. Interestingly, AES-S and AES-I displayed somewhat divergent results. Maybe this is explained by MCI cases underreporting compared to informants. An argument strengthened by the larger median for AES-I compared to AES-S in the MCI group, but not in the CU group.

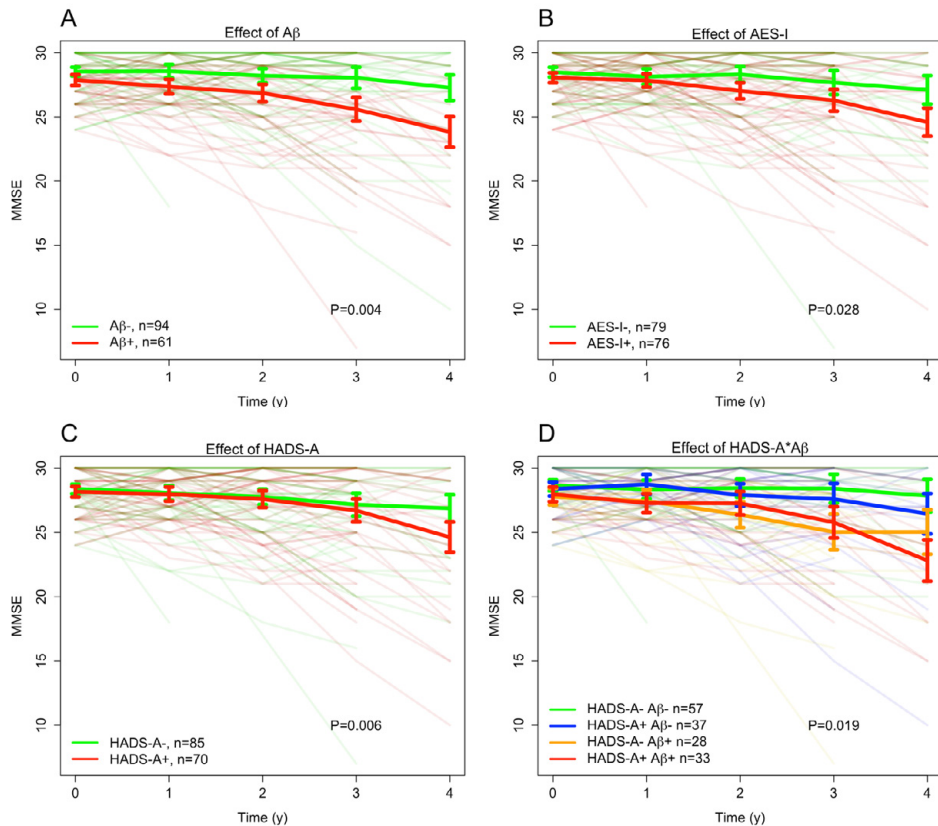


Figure 10. Effects of $A\beta$ and NPS on longitudinal MMSE

LME models corrected for age, sex, and education. Individuals were grouped according to $A\beta$ status (a pre-established cut-off of >1.42 SUVR on $A\beta$ -PET) and/or NPS status (using a median split). Panel A) Effects of $A\beta$ status on MMSE. Panels B-C) Effect of apathy and anxiety status on MMSE. Panels D) Interactions between anxiety and $A\beta$ status. P-values of the overall effect were obtained by restricted maximum likelihood ratio tests.

Paper III

Sample

The sample in paper III encompassed 55 A β -positive CU individuals from the BF-II cohorts A-C, representing preclinical Alzheimer's pathological change or preclinical AD according to the NIA-AA research framework. 25 of the participants were recruited as SCD but regarded as CU by the reasons described in the method section. 10 MBI-C item data points out of 1 700 were missing. These were dropped in the primary analyses by simply calculating MBI-C total scores by summing up the available item responses. However, for robustness, we also handled missing data by a single imputation procedure. Findings from secondary analyses on the imputed data set were found similar to the not imputed data set.

Main results

MBI-C total scores (a proxy for the overall burden of NPS) were cross-sectionally associated with the level of tau deposition in the composite ROI representing Braak stage I-II (including the entorhinal cortex and hippocampus), as well as the level of CSF P-tau181. MBI-C total scores were not related to tau in the composite ROIs representing the more advanced Braak stages III-IV or Braak V-VI. These findings aligned with the whole-brain voxel-based analysis (Figure 11).

Intriguingly, the episodic memory test ADAS-DR was associated with tau load in the Braak I-II regions only at a trend level ($p=0.065$). Also, in the regression models where both MBI-C and ADAS-DR were entered simultaneously to control each other, only MBI-C remained associated with tau deposition. Similar results were obtained when analyzing CSF P-tau181.

Conclusion

In preclinical AD, the overall level of MBI is associated with tau independently from memory deficits. This denotes MBI as an important early clinical manifestation related to tau pathology in AD.

Comments

The results in paper III contrast findings from an earlier tau-PET study on CU subjects. However, their sample was unspecified regarding A β status²⁴⁹. As abnormal tau deposition is essentially only found in the context of A β -positivity⁵⁸, this previous study might have suffered from low statistical power. Better aligning with the results in paper III, another previous study found an association between tau, especially in the entorhinal cortex, and multiple behavioral features (including neuroticism and openness, apathy, and depression) among CU at increased risk of

AD due to a positive family history of sporadic disease²⁶⁵. Combined, these studies indicate the importance of careful sample selection.

Tau deposition in the entorhinal cortex and the hippocampus is known to occur early on in AD^{3,58}, hence confinement of associations in these regions align with the use of a CU sample. Nonetheless, disturbances in drive and emotions are rarely related to temporal structures. Instead, they are often reported as manifestations of frontal lobe pathology. However, most pathological studies displaying such frontal associations have been conducted on MCI or AD demented stages^{263,266}. Bridging, the results in paper II, resting upon CU and MCI participants, argue for apathy to be related to temporal atrophy, but also, to a lesser extent, frontal atrophy. Moreover, the entorhinal cortex and hippocampus are highly interconnected with amygdala^{374,375}, a region important for emotional processing. Hence, it could be hypothesized that early temporal tau deposition in Braak I-II regions has an indirect but close effect on emotions via disruption of the emotional brain network.

The finding that MBI is associated with tau pathology, but only at a trend level with memory deficits, in a cohort of CU individuals further lends support to the ISTAART-AA MBI criteria that proposes that MBI can precede MCI¹⁰.

This study also has its limitations. First, the cross-sectional approach makes it difficult to fully explore the temporal order of appearance of NPS and cognitive deficits. Second, the sample size is modest, which needs to be considered when the results are interpreted. Third, ADAS-DR might not be sensitive enough to detect the most subtle change in memory performance among otherwise CU subjects.

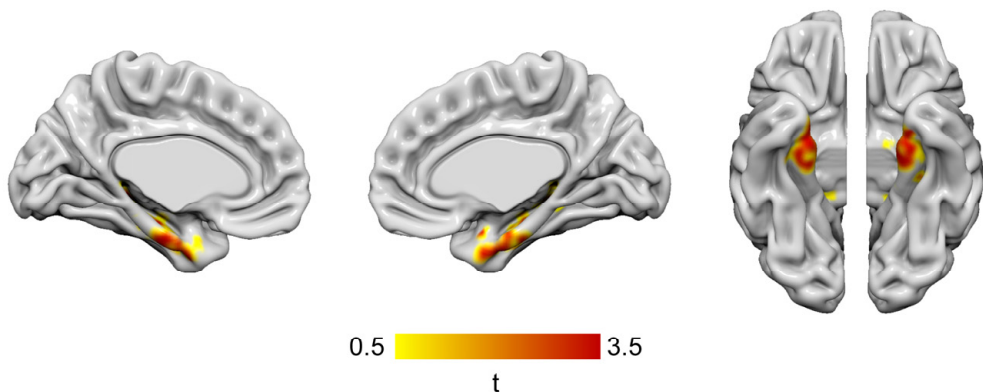


Figure 11. Whole-brain voxel-based analysis between MBI-C scores and tau-PET in CU Aβ+ subjects.

Voxel-based associations between Mild Behavioral Impairment-Checklist total scores and [¹⁸F]RO948-PET SUVR in 50 Aβ-positive cognitively unimpaired subjects. Statistical significance was determined using an extent threshold of 50 voxels. Models were adjusted for age, sex, years of education, and volume of white matter lesions. Correction for multiple testing was applied to parametric images using false discovery rate (FDR) $P < 0.05$. Associations were confined to the entorhinal cortex and hippocampus and, to a smaller extent, the anterior fusiform gyrus.

Paper IV

Sample

In this longitudinal study on the development of NPS, CU controls from BF-I were recruited. Only individuals with at least one NPS rating during the biennial follow-up of up to 8 years were included (n=356).

Main results

The main findings were that i) lower baseline CSF A β 42/40 (i.e., more pathology) had an increasing effect over time on the development of AES-I or HADS-A scores (i.e., more apathy or anxiety) (Figure 12), ii) over time steeper cognitive slopes (obtained by mPACC5 or MMSE) exerted rising effects on longitudinal AES-S or AES-I scores (Figure 13) and iii) the association between CSF A β 42/40, interacting with time, and longitudinal AES-I was partly (23%) mediated by the cognitive slopes (Figure 14). Importantly, the effect of baseline CSF A β 42/40 over time on longitudinal AES-I scores also remained after controlling for the cognitive slopes, indicating a remaining statistically direct effect by A β , independent of cognitive functioning. Effects over time by tau, neurodegeneration, WML, or baseline cognition on longitudinal NPS were not significant after correction for multiple comparisons. Neither neuropathology nor cognitive measures were related to longitudinal depression scores.

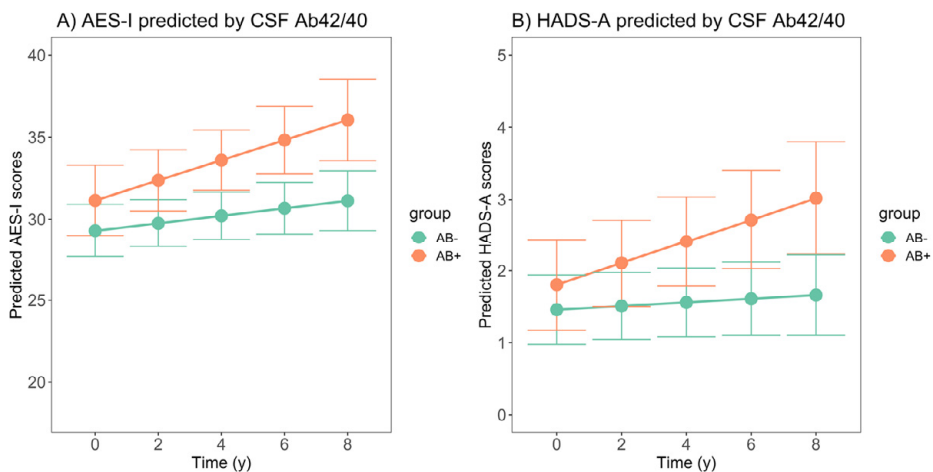


Figure 12. Effects of baseline A β pathology over time on the development of apathy and anxiety

Plots of estimated marginal means and 95% CI of the means obtained from LME models displaying significant effects by neuropathology over time on the longitudinal measures of NPS. Longitudinal measures of AES-I (panel A) (274 participants) and HADS-A (panel B) (321 participants) were separately entered as the dependent variable. Interaction terms between time and A β 42/40 were entered as a fixed effect corrected for age, sex, and education and included random slopes and intercepts. Participants were grouped according to a CSF A β 42/40 cut-point of 0.066 obtained by mixture modeling.

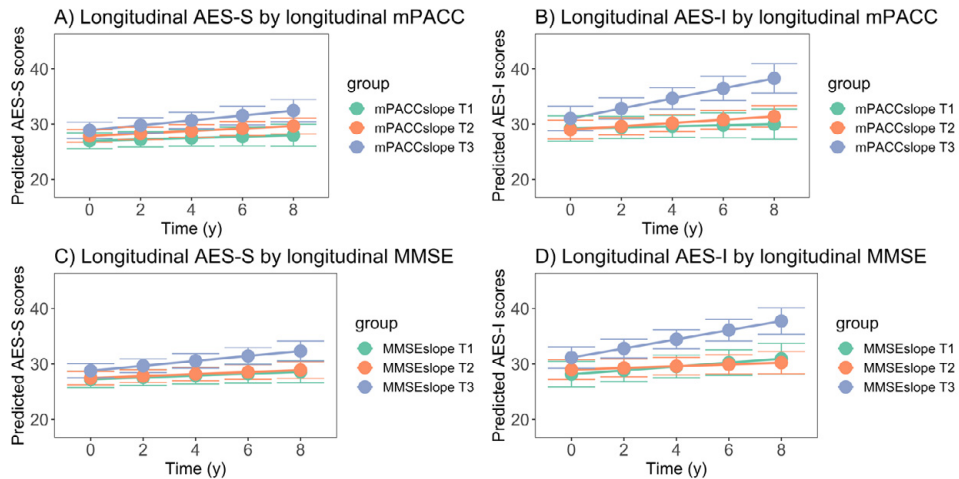


Figure 13. Effects on longitudinal neuropsychiatric measures by longitudinal cognition over time

Plots of estimated marginal means and 95% CI of the means demonstrating significant effects (also after adjustment for multiple comparisons) on longitudinal measures of neuropsychiatric symptoms by longitudinal cognition. In LME models longitudinal NPS measures of apathy (longitudinal AES-S by longitudinal mPACC5 [N=333], longitudinal AES-S by longitudinal MMSE [N=333], longitudinal AES-I by longitudinal mPACC5 [N=300], longitudinal AES-I by longitudinal MMSE [N=300]) were respectively entered as the dependent variable. Interaction terms between time and mPACC5 slopes (change per year) (panel A & B) or MMSE slopes (panel C & D) were entered as fixed effects in separate models. Participants are grouped according to tertials of the fixed effect variable using tertials (T1, T2, T3 [the higher figure, the more cognitive deficits]). All models were corrected for age, sex, and education and included random slopes and intercepts.

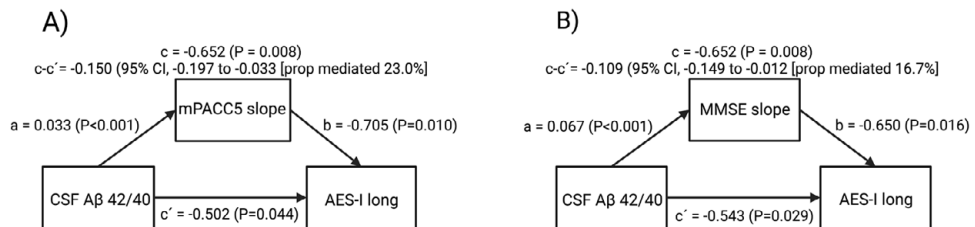


Figure 14. Cognition as a mediator between neuropathology and longitudinal neuropsychiatric symptoms

Mediation analyses of the relationship between neuropathology, cognition, and longitudinal NPS in initially CU participants. Only regression models in the primary analyses displaying significant associations between measures of longitudinal NPS (AES-I), baseline neuropathology (CSF A β 42/A β 40), and cognitive slopes (mPACC5 and MMSE) were used. The direct effect I of baseline CSF A β 42/A β 40 on the development of AES-I was obtained using LME models. The mediated effect of cognitive slopes (measured with mPACC5 [panel A] or MMSE [panel B]) is designated $c-c'$. The remaining effect of baseline CSF A β 42/A β 40 on longitudinal AES-I is designated c' . The direct effect of baseline CSF A β 42/A β 40 on the mediator mPACC5 or MMSE is a , and was obtained using linear regression modeling. The direct effect of baseline CSF A β 42/A β 40 on the development of AES-I is b . Models were corrected for age, sex, and education. All variables were zero-centered. LME models included random slopes and intercepts. Confidence intervals for mediation effects were obtained using bootstrapping with 1000 iterations.

Conclusion

Early A β -pathology may be a significant driver behind the development of both apathy and anxiety in early stages of AD. The effect of A β pathology over time on longitudinal apathy is only partly conveyed by worse cognition, hence A β pathology may influence apathy directly and somewhat independent of cognitive change.

Comments

Beyond merely determining links between NPS and AD pathology or cognitive impairment, the longitudinal nature of this study allowed some of the directions of these associations to be revealed.

As the prevalence of NPS is known to rise with worsening cognition, the findings in paper IV strengthen the proposed idea that cognitive deficits and NPS can develop primarily independently but nevertheless parallel to each other, given a common underlying neuropathology. However, the results in this paper, together with the results in paper II, further indicate that cognitive deficits and NPS to some extent also can reinforce one another²¹². The neuronal mechanisms behind the adjacent development of NPS and cognitive impairment, as well as their impact on each other, need further exploration. Perhaps they share a common anatomical location of AD pathology but arise from dysfunction in separate yet interconnected functional brain networks.

Baseline cognitive test performance could not predict NPS development in this study. However, NPS status could predict cognitive decline in paper II. Taken together, this highlights the potential clinical utility of early monitoring of NPS as prognostic markers for disease progression. However, the findings in paper II rest upon a mixed sample of CU and MCI, which limits the interpretation somewhat.

The strength of this study is its well-characterized sample and its longitudinal measures of both NPS and cognition. Nevertheless, there are also limitations. First, there were also here missing NPS data. However, besides from LME models being tolerant with missing data, supplementary sensitivity and survival bias analyses argued against a strong effect of bias due to missingness. Second, the NPS data rests upon assessments, not clinical diagnoses, and major psychiatric illness at baseline constituted an exclusion criterion. As in paper II, this limits the generalizability towards CU with only subsyndromal NPS or good mental health. Third, findings are not controlled for a history of psychiatric illness, although we did control for antidepressants during study follow-up. Fourth, tau and neurodegeneration are believed to develop somewhat later than A β in AD. As expected, biomarker levels of tau pathology and neurodegeneration in this study on CU are therefore low, which may have reduced the power to detect early associations with tau or neurodegeneration. Finally, pathology other than those studied in paper IV could have contributed to the evolution of NPS.

Concluding remarks

Taken together, the covered papers in the thesis display apathy, anxiety, and the overall burden of MBI to be associated with important hallmarks of AD, such as A β , tau, neurodegeneration, or cognitive deficits. The results further provide evidence for the direction of some of these associations. In paper II, we demonstrated that an increased apathy or anxiety status is related to future cognitive decline. In paper IV, we reported A β to be a significant driver of increasing apathy or anxiety levels, and this partly independent from cognitive decline. However, current levels of depression were associated neither with AD pathology nor cognitive impairment.

Clarifying the complex interplay between these variables can be argued crucial for efficient trial study design in AD⁸. Yet more, the findings also indicate the clinical usefulness of detecting NPS. The results in paper II, point to the value of recognizing early development of apathy or anxiety, as they appear to be risk markers of a worsening cognition. In paper III the analyses demonstrate that MBI, already in individuals without objective cognitive deficits, can predict early AD-related tau deposition, and hence may even precede memory difficulties.

Aiding both research and clinical management, the findings in paper I indicate that the developed Swedish version of AES provides a psychometrically favorable assessment of apathy levels in older adults, with or without a potential underlying ND.

The central findings in the thesis have, in general, support by the previous literature. However, as there is considerable heterogeneity between reports in some areas of this scientific field, more work will be needed until a definite neurobiological signature of NPS in AD can be ultimately decided.

Future directions

To further disentangle the temporal and causal relationships between AD pathology, NPS, and cognition, the research field would benefit from more longitudinal studies as well as harmonization of study protocols. In parallel, future studies should also put more effort into demonstrating and operationalize the potential clinical utility of NPS. Three important areas of such work can be envisioned; i) recognition of early NPS due to AD in medical units not primarily oriented towards NCD, ii)

improvement and organization of the overall clinical management of NPS, and iii) use of NPS in clinical AD criteria.

Harmonization of neuropsychiatric symptom study protocols

The many conflicting observational reports, as well as the limited treatment options for NPS in AD, may well reflect the methodological heterogeneity and challenges in designing studies in this field of research. The span of methodological approaches is vast.

First, sample selection varies according to the cognitive stage of interest^{251, 252, 255, 270, 376}, their definitions²¹¹, and supposed etiology. Only a few studies have investigated samples with biomarker evidence of having AD^{6, 281}. Such samples, at least when investigating clinical stages, might reduce confounding by coexisting pathologies also associated with NPS. Additionally, when addressing preclinical stages of the disease, biomarker confirmation of AD pathology could probably increase the statistical power to detect more subtle associations between early NPS and AD-related pathologies that follows upon A β , α , tau or neurodegeneration.

Moreover, NPS (e.g., major depression) are suggested to impact cognition negatively³⁷⁷, which subsequently increases the risk of misclassification regarding cognitive stage and potentially introduces sampling bias²⁷⁶. For instance, individuals with MCI due to AD might be misclassified as demented given the additional load of major depression, rendering exclusion from the study. Depressed participants without an incipient ND can also mistakenly be included as MCI participants. When exploring rates of cognitive decline, a subsiding depressive episode with recovered cognition could then statistically parade as a health marker rather than a risk marker²⁴⁵.

Second, NPS is defined and assessed differently. Some report on NPS status by dichotomizing rating scale total scores^{216-219, 237, 241}, while others use diagnostic criteria^{220, 244, 245, 276, 378}. The proposed criteria specific for certain NPS in AD have rarely been used^{185, 198}. In some studies, associations between AD and a history of a past psychiatric disorder are explored^{275, 379, 380}, whereas most studies address the current level of NPS manifestations^{155, 211, 241, 266, 267}. Additionally, the rating scales used, as well as their rater sources, differ^{155, 211, 241, 266, 267, 381}. Furthermore, some studies explore the global level of NPS^{216, 219, 221, 222, 382}, while others explore individual NPS^{155, 211, 241, 267, 381}.

Third, the use of AD biomarkers has changed as technical advances have been made. Previously most studies rested upon CSF data, but today many investigators of NPS have turned to PET imaging. Even if the data generated from these techniques in many ways are related, both have their unique set of methodological challenges³⁸³⁻³⁸⁸, and seem to reflect on slightly different aspects of neuropathology and its development⁷⁶.

Fourth, consideration of the evolution and fluctuating nature of NPS varies. Most studies have adopted cross-sectional approaches^{155, 211, 266, 267}. Yet, longitudinal datasets are evolving, and give opportunity to address the directions of certain associations, as well as to control for the fluctuations of NPS over time. However, depending on the length of follow-up or the interval between assessments, longitudinal studies might have different likelihoods of detecting changes over time, possibly leading to different outcomes^{265, 280}. Importantly, some commonly used rating scales in the field are yet not proven to detect changes over time, e.g., for apathy³⁸⁹. Moreover, the length of follow-up might be of particular importance for intervention studies. The underlying pathologies of AD continuously progress in their detrimental effects on the brain. Intervention studies must therefore balance the need for a duration long enough to register a potential clinical effect on NPS, but still not so long that the ability to demonstrate an actual effect is compromised by the general disease progression³⁸¹. Additionally, trials need to decide where along the clinical AD continuum the drug is most likely to be efficient. Most intervention studies have addressed AD demented stages of disease when the brain injury is more profound^{241, 298}, and intervention in CU or MCI stages is less studied²⁹⁷.

Fifth, confounding factors are handled differently. Some have controlled for the significant overlap between certain NPS, such as apathy and depression, whereas many have not^{224, 266}. Other potentially critical confounders are ongoing pharmacological treatments, past or present psychiatric comorbidity, or the presence of other coexisting degenerative or vascular diseases of the brain³⁸¹.

To conclude, although the use of different methodologies has its advantages, too widely spread approaches can also add confusion and hinder comparisons between studies. It could be argued that future observational and intervention studies in the research field surrounding NPS in AD would benefit from harmonization of methods. Previous attempts have been made to formalize recommendations for study protocols encompassing clinical studies of apathy in AD¹⁰⁹. The field could now benefit from an update of these recommendations, extended to NPS in general and preferably authorized by an international working group.

Recognition of AD-related neuropsychiatric symptoms

The reported high prevalence of primary psychiatric diagnoses among not yet clinically diagnosed patients with AD¹⁵⁹, infers that these individuals seek initial healthcare in primary care settings or are early on referred to specialized medical centers not primarily oriented towards NCD, as psychiatry or geriatric medicine.

Future studies should aim to confirm these limited reports and further describe the various routes of seeking health care among AD patients. If it holds true that MBI/NPS can precede the cognitive deficits in AD and further that some AD patients consequently are initially handled in non-cognition oriented health care centers, the

medical routines in these settings might need to be revised in order to provide the patients with an as early and accurate diagnosis and management as possible.

The over-all clinical management of neuropsychiatric symptoms

While awaiting an AD disease-modifying treatment, the ultimate goal of the clinical care of AD patients and their caregivers is to sustain or regain a good quality of life.

Despite being demonstrated common and related to several negative outcomes¹⁷⁴⁻¹⁷⁸, NPS is clinically often underrecognized^{8, 157, 158}, with a missed opportunity of possible pharmacological and psychosocial interventions^{109, 297, 300, 390, 391}, as well as an overall structural management of NPS³⁹²⁻³⁹⁴.

An excellent example of recognizing NPS also in the early stages of the disease is the *Behavioral symptoms in Alzheimer's disease Towards early Identification and Treatment* (BEAT-IT) study. This study aims to structure and standardize early detection of NPS, implement current guidelines for NPS treatments, and investigate the effect of these interventions on quality of life¹⁵⁶.

Neuropsychiatric symptoms in future Alzheimer's disease criteria

In diagnostic criteria for AD (e.g., DSM-5 or the latest IWG criteria^{13, 84}), cognitive deficits in comparisons to NPS will inevitably contribute with a higher specificity towards underlying neuropathology and better predict clinical progression. NPS falls short as they occur not only in ND but also in several primary psychiatric disorders or even in normal psychological reactions. Furthermore, NPS is more difficult to objectively and reliably quantify^{395, 396}. Accordingly, it can be argued reasonable that clinical or clinical-biologically oriented diagnostic criteria historically have emphasized the role of cognitive deficits rather than NPS.

However, as criteria over time tend to be viewed not only as diagnostic tools but also mere descriptions of the disease in general, an absence of NPS in AD criteria may lead to them being clinically overlooked. This despite their known relation to clinically adverse outcomes. Moreover, as modern AD biomarkers have grown increasingly specific, future clinical-biological criteria could perhaps allow integration of NPS in their clinical parts. This at the expense of a somewhat lower specificity but in favor of an assumed increased sensitivity at least in the very earliest stages of the disease. Such criteria would also allow individuals with established AD pathology and NPS, but not cognitive deficits, to acquire a diagnosis of AD and subsequently enable them appropriate treatment and management.

To facilitate and further legitimize the incorporation of NPS in clinical-biological criteria, future work should establish better definitions for certain NPS in an AD context (e.g., depression in AD), provide even more robust NPS ratings with optimized cut-offs, and systematically study the added value of NPS in such criteria.

At last, development of a biologically oriented yet clinically applicable AD definition, not anchored in clinical manifestations, would paradoxically open the possibility to recognize the early and complete AD clinical syndrome once more.

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