Charles University
Second Faculty of Medicine

Doctoral study programme: Neurosciences

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Associations of morphometric and metabolic biomarkers with cognitive impairment in Alzheimer's disease and Lewy body dementias.

Asociace morfometrických a metabolických biomarkerů s kognitivním postižením u Lewy body a Alzheimerovy demence.

Dissertation Thesis

Supervisor: prof. MUDr. Jakub Hort, Ph.D.

Prague 2023

Prohlášení

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V Praze, 22.05.2023

Zuzana Nedelská

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Acknowledgement

The work presented in this dissertation reflects the development between 2010 and 2022 from working as neurology resident in general wards and outpatient clinic to laboratory assistant to PhD student. From the field of spatial navigation research to brain imaging using magnetic resonance to molecular imaging and from Alzheimer's disease to dementia with Lewy bodies. Transitioning from the healthcare and clinical research in the Czech republic to translational clinical research and its organization in an American institution and returning to Prague. The work was not straightforward, it was quite convoluted.

I need to thank prof. Jakub Hort, Ph.D., who accompanied me from the beginning as a supervisor and the head of the Cognitive center, Department of Neurology, Motol University Hospital in Prague. My thanks is for support and feedback, providing me with the free space I needed, and for helping me to get institutional support my first fellowship in the United States.
Many thanks to all my colleagues at the Cognitive center and the Brno site of the study for their insightful comments throughout the research and for their excellent work in general and ability to stay resilient and motivated.

I want to thank prof. Kejal Kantarci, M.D., M.S. from the Alzheimer's Disease Research Center, Department of Radiology, Mayo Clinic Rochester, for introducing me to the field of dementia with Lewy bodies, which I am continuing to be very much involved in to this day, for mentoring me and providing me with background in clinical research methodology and multimodality brain imaging during ageing and dementia.

Also, thanks to my dear friend and colleague Prof. Bing Zhang, M.D., Ph.D. from Nanjing medical school for sharing the support lasting from our fellowship at the Mayo Clinic to our collaborative research and many publications while mentoring her talented students.
Thanks to all other positive influences in the background.

The work was supported by the International Clinical Research Center Brno - LQ1605, The Radiology Research Award Mayo Clinic, IBRO Fellowship, GAUK 624012, AZV NV18-04-00346 and NU21-04-00535, Czech Alzheimer Foundation, Project LX22NPO5107 MEYS – Next Generation EU, and Charles University grant UK PRIMUS 22/MED/011.

Associations of morphometric and metabolic biomarkers with cognitive impairment in Alzheimer's disease and Lewy body dementias

Abstract

Dementia has become one of the major health care and socio-economic challenges. Alzheimer's disease (AD) is the most common dementia whereas dementia with Lewy bodies (DLB) is the second most common neurodegenerative after AD. However, both dementias exist in a quite heterogeneous contiua that can overlap with each other. Approaches that allow for the identification of individuals at risk of developing AD in preclinical or prodromal stages are of major interest to apply the symptomatic and newly introduced biological therapies and non-pharmacological interventions that are more effective early on. Similar efforts are undertaken in the DLB field although no causal treatment for DLB is available yet. A prerequisite for an efficacious and targeted intervention is a selection of individuals who would benefit the most from this intervention. This process includes the timely and accurate diagnosis, differential diagnosis, prognostication, and management of treatable comorbidities. This dissertation has two parts. Part one is an overview of AD and DLB. The second part summarizes author's research work. The main research aims corroborated in this thesis are three-fold: First, to utilize experimental neuropsychology tests as potential markers of early AD stages and to determine their clinico-anatomical associations with brain imaging. Second, to describe cognitively normal older adults who may be at risk of developing clinically apparent AD using widely available brain imaging method that could predict positivity of well-established but expensive and invasive metabolic AD biomarkers. Third, because AD frequently overlaps with DLB, causing the diagnostic challenges and DLB patients to progress faster and survive shorter, work also aimed at using multimodality imaging in DLB to disentangle the DLB-related and AD-related imaging findings and their associations with clinical phenotype and disease progression.

Keywords

Alzheimer's disease dementia, biomarkers, dementia with Lewy bodies, magnetic resonance imaging, mild cognitive impairment, mixed pathologies, morphometry, positron emission tomography, prodromal, spatial navigation

Asociace morfometrických a metabolických biomarkerů s kognitivním postižením u Lewy body a Alzheimerovy demence

Abstrakt

Syndrom demence představuje významnou zdravotnickou a socioekonomickou výzvu. Alzheimerova choroba (AD) je nejčastější příčinou demence. Demence s Lewyho tělísky (DLB) představuje druhou nejčastější neurodegenerativní demenci. Obě demence jsou však heterogenní množiny vyvíjející se v klinicko-patologickém kontinuu, přičemž tato kontinua se mohou vzájemně překrývat. Metody, které by umožnily vytipování či přímou identifikaci osob s rizikem rozvoje AD demence či DLB v časných klinických nebo dokonce preklinických stadiích jsou v centru zájmu. Včasné nefarmakologické a symptomatické farmakologické intervence či nově vyvíjené biologické formy terapie AD jsou účinnější v časnějších stadiích než u klinicky plně rozvinutého syndromu demence. Předpokladem pro efektivní intervenci je její zacílení na nejvíce vnímavou populaci, včasný záchyt, diferenciální diagnostika, pochopení průběhu nemoci a léčba komorbidit. První, obecná, část disertace je formou přehledného referátu o AD a DLB. Druhá, výzkumná, část práce shrnuje výsledky výzkumu autorky disertace. Hlavní cíle výzkumné práce byly tyto tři: za prvé, aplikace testů experimentální neuropsychologie jako potenciálních markerů časných stadií AD a jejich klinicko-anatomické asociace se zobrazovacími metodami mozku. Za druhé, charakterizace starších osob v riziku rozvoje klinické AD pomocí běžně dostupné zobrazovací metody, která může predikovat pozitivitu etablovaných, ale finančně náročnějších a poměrně invazivních AD biomarkerů. Za třetí, vědecky podložené použití multimodalitních zobrazovacích metod v časné a přesnější diagnostice DLB pacientů, kteří mají často také AD jako ko-patologii. Tento jev vede k diagnostickým nejasnostem, a pro pacienta a blízké představuje rychlejší progresi nemoci, náročnější a pestřejší symptomy a kratší dobu přežití.

Klíčová slova

Alzheimerova choroba, biomarkery, demence s Lewyho tělísky, smíšené patologie, magnetická rezonance, mírná kognitivní porucha, morfometrie, pozitronová emisní tomografie, prodromální, prostorová navigace

List of abbreviations

Aβ = amyloid-β

AD = Alzheimer´s disease

ADdem = Alzheimer´s disease dementia

ADRC = Alzheimer's disease research center

ALS = amyotrophic lateral sclerosis

aMCI = amnestic mild cognitive impairment

ANOVA = analysis of variance

ANCOVA = analyses of covariance

APOE ε4 = apolipoprotein E alela ε4

ASL = arterial spin labeling

AVLT = auditory verbal learning test

AUC = area under the ROC curve

BF = basal forebrain

CAA = cerebral amyloid angiopathy

CBAS = the Czech Brain Ageing Study

CBD = corticobasal degeneration

CDR = clinical dementia rating

CDR-SOB = clinical dementia rating sum of boxes

CERAD = Consortium to Establish a Registry for Alzheimer's Disease

CI = confidence interval

CIS = cingulate island sign

CISr = cingulate island sign ratio

CN = cognitively normal

CSF = cerebrospinal fluid

CU = cognitively unimpaired

DLB = dementia with Lewy bodies

DATscan = Dopamine Transporter Scan, ioflupane I^{123} SPECT

EEG = electroencephalography

eTIV = estimated total intracranial volume

^{1}H-MRS = proton magnetic resonance spectroscopy

FDG PET =16-fluoro-d-deoxyglucose positron emission tomography

FLAIR = fluid attenuated inversion recovery T2-weighted MRI sequence

FTD = frontotemporal dementia

FTLD = frontotemporal lobar degeneration

HGT = hidden goal task

IQR = interquartile range

LATE = limbic-predominant age-related TDP-43 encephalopathy

LBD = Lewy body disease

MCI = mild cognitive impairment

MCSA = Mayo Clinic Study of Ageing

mI = myo-inositol

MMSE = mini mental state examination

MRI = magnetic resonance imaging

MSA = multiple systemic atrophy

MTL = medial temporal lobe

MWM = Morris water maze

NAA = N-acetyl-aspartate

NbM = nucleus basalis of Meynert

NC = normal control

NDD = neurodegenerative diseases

NIA-AA = National Institute of Ageing and the Alzheimer's Association

OR = odds ratio

pASL = pseudo-continuous arterial spin labeling

PART = primary age-related tauopathy

PCA = posterior cortical atrophy

pCASL = pseudo-continuous arterial spin labeling

PDD = Parkinson disease dementia

PPA = primary progressive aphasia

p-tau = phosphorylated tau

PET = positron emission tomography

PiB = ^{11}C-Pittsburgh compound B

PSP = progressive supranuclear palsy

PSG = polysomnography

RAVLT = Rey Auditory Verbal Learning Test

RBD = REM sleep behavior disorder

ROC = receiver operating characteristic

ROCFT = Rey-Osterrieth Complex Figure Test

SCD = subjective cognitive decline

SD = standard deviation

SE = standard error

SEM = structural equation modeling

SUVR = standardized uptake value ratio

TDP-43 = transactive response DNA binding protein of ~43 kD

VaD = vascular dementia

VBM = voxel based morphometry

VH = visual hallucination

WMH = white matter hyperintensity

$\chi 2$ = test chi-squared tes

Content

1. INTRODUCTION

1.1. The age landscape and dementia

As the popoluation word-wide ages, the number of older people, including those with dementia, is increasing.

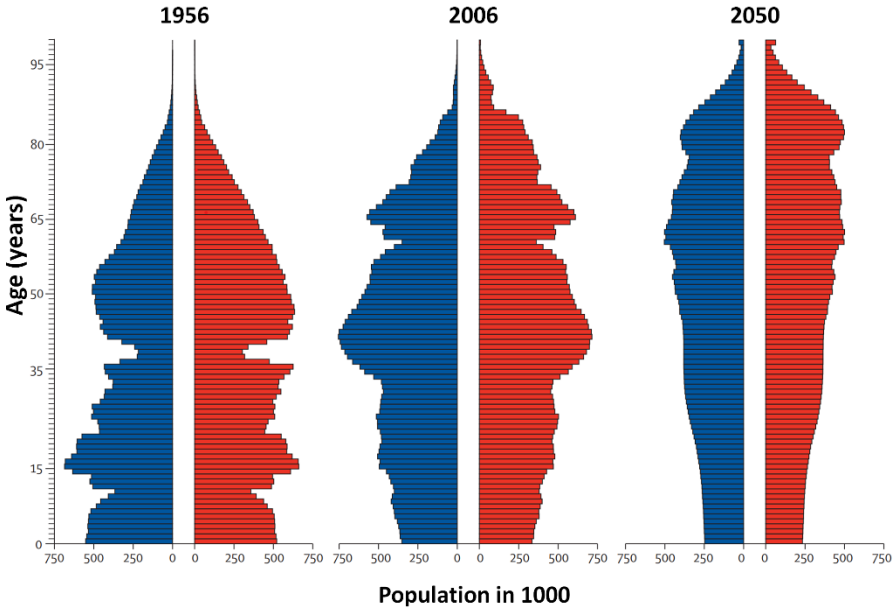


Figure 1. Population pyramid for Germany: 1956, 2006, and 2050 projection. Germany shares similar population landscape with Czechia. The horizontal bars represent the number of men (blue) and women (red). Projections for 2050 are based on German Federal Statistical bureau, assuming a life expectancy in 2050 of 88,0 years for women and 83,5 years for men, roughly constant total fertility rate 1,4 and annual net migration of 100.000. Adapted from Christensen K., et al., The Lancet 2009 (Christensen et al., 2009).

Age is the primary risk factor for dementia. According to *The Alzheimer's Disease International* organization's document World Alzheimer Report 2021 (https://www.alzint.org/resource/world-alzheimer-report-2021/), over 55 million people lived with dementia world-wide in 2020. Projections of *The World Health Organization* suggest this figure will be 78 million by 2030, and 140-150 million by 2050. In the Czech Republic, 160 thousand people lived with dementia in 2020 according to *the Czech Alzheimer Society* annual report, women being affected almost twice as often as men. The estimated figure of individuals living with dementia in the Czech Republic is 290 thousand by 2050, which equals the population of the Czech's third largest city of Ostrava. Dementia is now the fifth leading cause of adult death in the first world countries, and constitutes an enormous social, healthcare, and economic burden. In the United States alone, direct payments for healthcare and hospice services were over 305 billion US dollars in 2020, with

overall costs estimated to be about staggering 1 trillion US dollars annually, reported by 2018 World Alzheimer Report 2018. In the next decades, however, lower income countries will drive the figure of people living with dementia world-wide.

In this work, solely two most common neurodegenerative dementias will be discussed. Other causes of dementia will not be discussed in detail. Alzheimer's disease (AD) is the most common cause of dementia in individuals over 65 years old, and the most common neurodegenerative dementia, accounting for 60-70 % of all cases. Dementia with Lewy bodies (DLB) is estimated to be the second most common neurodegenerative dementia (Vann Jones & O'Brien, 2014; Zaccai et al., 2005) after AD. Many individuals, and most individuals over 80 years old, however, have more than one cause contributing to their dementia. The causes, be it neurodegenerative or other, are often overlapping. This overlap of pathologies can obscure the typical findings of a disease or modify the course of the disease, or diversify the symptoms experienced by the patients. Overlapping pathologies are a major diagnostic and differential diagnostic problem, as well as a challenge with prognostication, treatment choices and selection of patients for clinical trials.

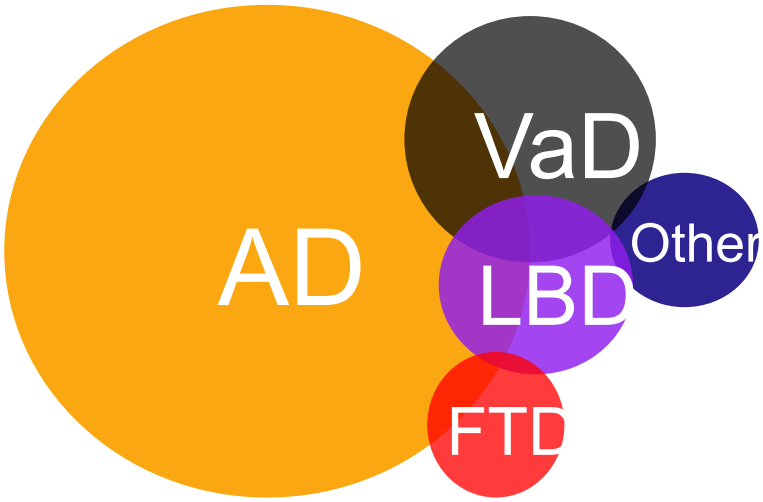


Figure 2. Venn diagram showing the major neurodegeneration dementia types (FTD is frontotemporal dementia). The estimated prevalence is depicted using the circle size. The vascular dementia (VaD) is included for its high frequency and impact. The figure is simplified and does show only major types of dementia.

1.1.1. Neurodegeneration and neurodegenerative disease

Neurodegenerative diseases (NDD) is an umbrella term for a wide range of conditions primarily affecting the neurons in the central and peripheral nervous system. Neurodegeneration can be characterized as a progressive loss of selectively vulnerable neuronal populations. This contrasts with a rather static neuronal loss due to toxic or

metabolic causes, although these can contribute or enhance the neurodegenerative cascade of events.

Classification of NDD is complex, and it is a dynamic process, with concurrently updated and newly arriving classifications and novel insights into the NDD. Classification of NDD can follow principal clinical features such as motoneuron disease or dementia or primary anatomical localization of process such as spinocerebellar or extrapyramidal disorders or frontotemporal degenerations. A common approach to classify neurodegenerations has been by the principal protein abnormality, thus naming them *proteinopathies*: tauopathies, amyloidopathies, α-synucleinopathies, TDP-43 proteinopathies, and prion diseases (Dugger & Dickson, 2017), to name the major classes.

Under certain conditions which are yet to be understood in detail, the proteins undergo abnormal conformational changes, and accumulate in the tissue. Moreover, there is a growing evidence that abnormal proteins may spread along anatomical pathways (and also functional networks). This may be reflected at autopsy by relatively specific and stereotypic patterns of abnormal protein localization.

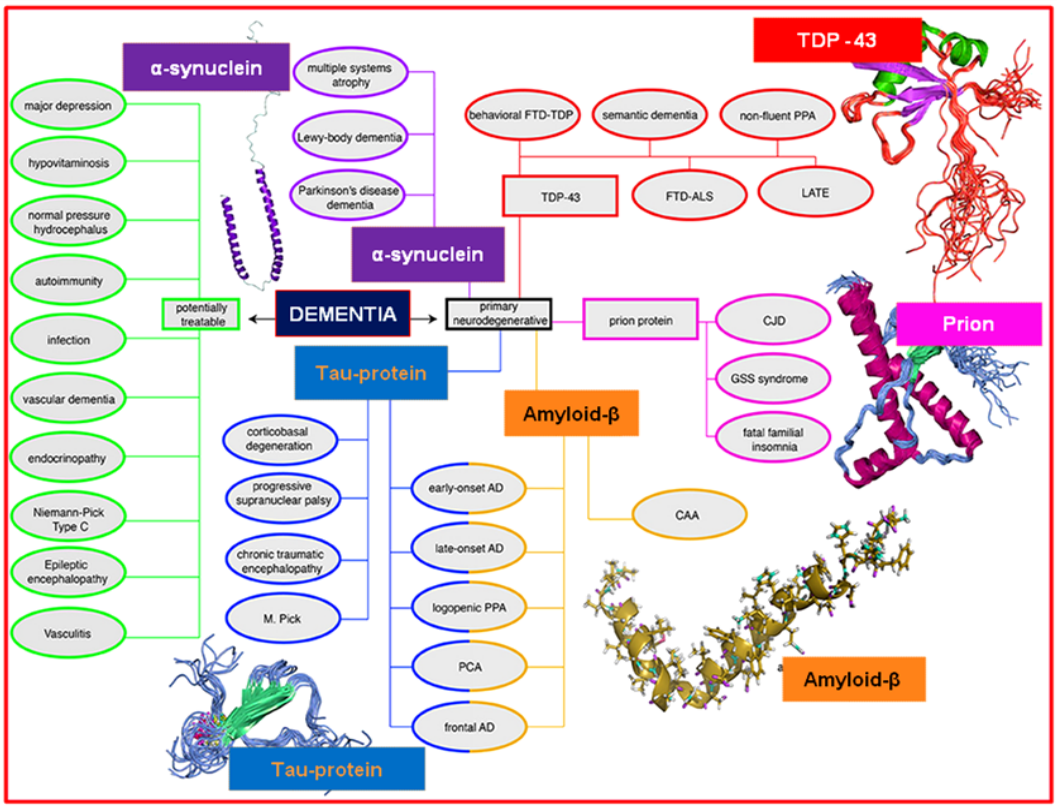
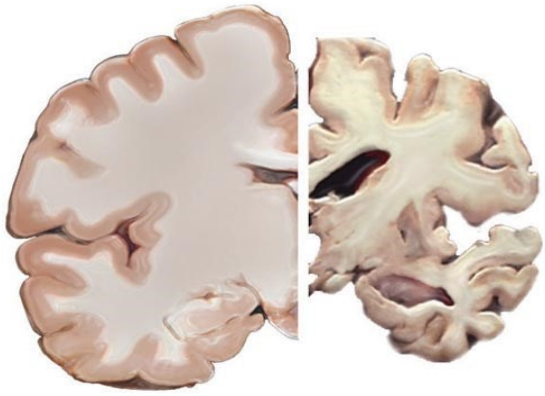


Figure 3. Schematic of dementia as a clinical outcome stemming from an array of potentially treatable aetiologies. Focus is on color-coded major proteinopathies, emphasizing the variety of primary neurodegenerative aetiologies and associated clinical entities. Adapted (Stefanovski et al., 2021).

The traditional paradigm has been that an accumulation of abnormal and neurotoxic proteins in the tissue causes in a step-wise fashion *a cascade of events leading to an abnormal metabolism, progressive loss of neurons, atrophy, and finally, the clinical manifestation of the proteinopathy*.

Various popular sources communicating information on NDD to both professional and general audience, display *Figure 4,* below, to emphasize the potential final outcome of this cascade comparing the autopsied normal brain on the left to the brain affected by the advancedstage of AD on the right (source https://en.wikipedia.org/wiki/Neurodegeneration).



This traditional paradigm of *neurodegeneration and atrophy coupling* may be satisfactory to describe the simplified cascade of events in AD, however, may not be entirely universal. For example, in ‚pure' DLB, a minimal brain atrophy has been observed, suggesting that deficits caused by abnormal α-synuclein accumulation may not be largely structural, but of different nature such as biochemical, or microstructural.

1.1.2. Gold standard in diagnosis of NDD: an autopsy

So far, the neuropathologic examination at autopsy has been the gold standard in diagnosis of NDD and assessment of the nature of abnormal protein deposits. Autopsy diagnostic criteria and related laboratory procedures have been formulated and re-updated for specific proteinopathies and for specific diagnostic entities such as amyloidosis, tauopathy and AD and others such as α-synucleinopathy in LBD, TDP-43 and prion particles in other NDD Although the neuropathologic understanding is critical to developing biomarkers to diagnose NDD and monitor them *in vivo*, the problem with timing and delivery of post-mortem diagnosis is obvious. (Mirra et al., 1991; Thal et al., 2002) (Dickson, 1997) (Hyman & Trojanowski, 1997);(Montine et al., 2012); (Mandelkow & Mandelkow, 2012) (Braak & Braak, 1991a; Grundke-Iqbal, Iqbal, Quinlan, et al., 1986; Grundke-Iqbal, Iqbal, Tung, et

al., 1986) (Braak et al., 2011; Crary et al., 2014); (Murray et al., 2011) (Spillantini et al., 1997) (Kosaka et al., 1984); (Braak et al., 2003) (McKeith et al., 2005) (Neumann et al., 2006) (Josephs et al., 2014) (Mackenzie et al., 2011; Prusiner, 1982) (Ellison et al., 2013) (Prusiner, 1998a, 1998b).

1.2. Normal and abnormal ageing continuum

The abnormal protein deposits, such as tau, ß-amyloid, argyrophilic grains, TDP-43 are found even in the brains of elderly who did not exhibit signs of cognitive impairment or dementia antemortem, especially in the oldest old. It is critical that the amount of abnormal protein deposits does not exceed a certain quantitative or time threshold to cause an apparent cognitive decline. Some of these individuals with normal cognition and functioning but abnormal protein deposits in their brains will go on to develop the fully symptomatic disease in the future, if they survive long enough, thus they have **a preclinical disease**. However, it has been extremely challenging to identify these at-risk individuals because there is a complex yet to be properly understood interplay of multitude factors determining the resilience of brain tissue to pathology (genetic, epigenetic, lifestyle, psychosocial, etc).

During **normal (physiological) ageing**, the changes occur in an ageing brain, and these changes are chemical, cellular-level, structural and functional. These changes do result in a cognitive decline that is detectable. The cognitive decline is across all cognitive domains. However, in normal brain ageing i.e., ageing, without a sufficient underlying brain pathology, the cognitive decline does never result in an impaired self-sufficiency. Therefore, both basic and instrumental activities of daily living are largely unimpaired, although learning of new, complex skills can be worsened.

On a macroscopic level, a reduction in brain volume and expansion of ventricles (i.e., atrophy) is observed on MRI by visual inspection or by quantitative volumetry (Resnick et al., 2003). Atrophy occurs both in grey and in white matter (Sowell et al., 2003). Some studies suggest faster brain atrophy in elderly men (Coffey et al., 1998). In men, subcortical white matter tends to recede faster (Coffey et al., 1998), whereas in ageing women, regional grey matter and cortical thickness tend to recede faster (Luders et al., 2006). During normal ageing, the overall neuronal loss is approximately 10%, a relatively smaller amount that does not sufficiently explain the cognitive decline (Pakkenberg & Gundersen, 1997; Pakkenberg et al., 1997). What does explain the cognitive decline in an ageing brain then?

On a microscopic level, the number of dendrites decreases, dendritic length shortens,

dysfunction and loss of synapses, and axonal demyelination (Pannese, 2011) occur in normal ageing. These microstructural changes, and especially synaptic loss, appear to drive the cognitive decline in normal ageing. Moreover, ageing is associated with a decline in several mediator systems such as acetylcholine or dopamine (Pakkenberg et al., 2003; Schliebs & Arendt, 2011). Similarly, metabolic and gene expression changes lead to a reduced brain plasticity and quality of cortical circuits (Burke & Barnes, 2006; Hof & Morrison, 2004).

Certain brain structures may be more sensitive and vulnerable to various changes occurring during brain ageing. The mesial temporal structures, prefrontal cortex, and basal forebrain are among the most vulnerable (Grothe et al., 2013; Grothe et al., 2012; Jack et al., 1998; Jack et al., 1997; Resnick et al., 2003).

Apart from brain tissue itself, brain ageing encompasses also variety of vascular changes such as decrease or loss of the blood-brain barrier integrity and hypoperfusion linked to, among other factors, an increased arterial stiffness, endothelial senescence, oxidative stress and inflammation and narrowing of the vascular lumen that renders vasculature vulnerable to atherosclerosis (Ungvari, Tarantini, Donato, et al., 2018; Ungvari, Tarantini, Kiss, et al., 2018; Yang et al., 2017).

On the functional and clinical level, in normal ageing, the decline is more gradual and insidious, and what can be labelled as age proportional. However, in **abnormal ageing**, the changes are typically accelerated even rapid, more profound, and progressive. The essence of the main clinical and functional differences between normal and abnormal ageing are listed in Table 1 adapted from Vyhnálek et al., 2021.

Table 1. Features of normal and abnormal ageing, continued the next page

	Normal ageing	**Abnormal ageing**
Progression of symptoms	Slowly progressive over the years with no significant worsening in the last year	Accelerated deterioration in the last year or rapid deterioration (typically vascular changes).
Cognitive impairment profile	Overall slight deterioration proportional to age, mild slowing down of psychomotor pace, mild decline in attention. Speech impairment is typically not detectable.	Different profiles, often disproportionate impairment of various cognitive functions, e.g., significant memory impairment, impaired logical judgement, speech

		impairment etc.
Memory impairment	Impaired capacity to learn new information. Once learnt information is though remembered. Frequent distractibility (looking for glasses, keys etc.)	Impaired learning ability is combined with significant forgetting once learnt especially recent, information. Basal ganglia impairment is associated with procedural memory impairment such as automatisms, motor skills.
Affective and behavioural changes	Gradual accentuation of personality traits.	Newly emerging significant mood or behaviour disorders, delusions etc.
Neurology assessment and motor impairment	Impairment is gradually developed and slowly progressive only in late age, often nonspecific gait and balance disturbances. Topical findings are mild and nonspecific.	Newly emerging or rapidly progressive impairment such as parkinsonism, axial syndrome, oculomotor or swallowing or other topical impairment.
Activities of daily living	Retained, although some difficulties may arise learning new complex skills such as driving motor vehicles, operating new equipment etc.	Detectable deterioration during a relatively short interval in previously normal daily activities.
MRI and biomarkers	Age-related atrophy on MRI is present but is minimally progressive. AD-related biomarkers from CSF and amyloid-PET are negative.	Atrophy on MRI can be profound and can be specific to regions such as medial temporal in AD. Vascular changes can be profound. Specific biomarkers are positive.

The changes associated with normal and abnormal ageing thus coexist in a **continuum of stepwise clinic-pathological changes** from the *normal ageing* to *subjective cognitive decline (SCD)* to *mild cognitive impairment (MCI)* to *fully developed dementia* that can be regarded for practical purposes as *mild*, *moderate,* and *severe dementia*. This continuum of changes could theoretically be applied to any underlying neurodegenerative cause, although the continuum has been most thoroughly researched and modelled for AD. The earlier stages (left side in the Figure 5) are potentially reversible, although the factors that are associated

with this reversibility are complex and more research is warranted. Lifestyle activities such as physical activity, specifically fieldwork or gardening (Shimada et al., 2019), interestingly, or Mediterranean diet (Dhana et al., 2021; Valls-Pedret et al., 2015) have been reported as modifiable factors positively associated with the reversibility of clinical decline in the early stages of ageing continuum.

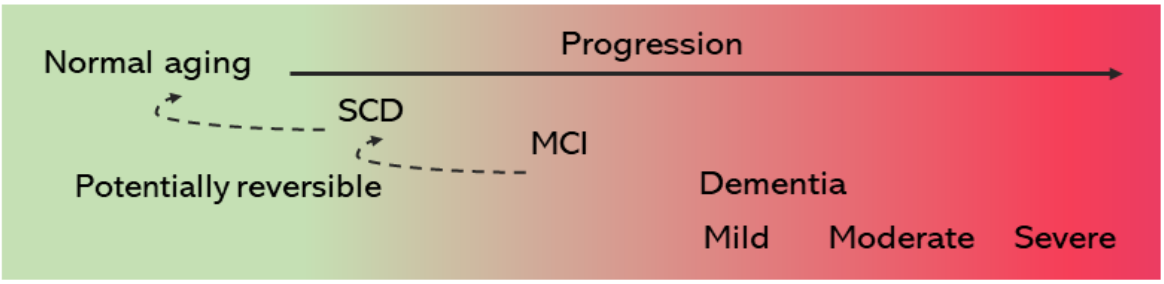


Figure 5. Schematic shows the cognitive continuum and the progression of the cognitive impairment from normal ageing through severe dementia. Dashed arrows point to potentially reversible stages where lifestyle factors, among others, play a role. It remains to be established whether new biological treatments for AD may revert dementia to milder cognitive impairment or revert, or stabilize, mild cognitive impairment from progression to dementia.

1.2.1. Subjective cognitive decline

The term SCD was first coined by Frank Jessen in 2014 (Jessen, 2014) in an effort for the timely diagnosis of neurodegenerative disorders, aiming at preclinical stages. Although SCD is a clinical concept, with several possible underlying aetiologies including neurodegenerative and non-neurodegenerative, it was particularly intended for AD, given the availability of *in vivo* AD-related biomarkers (Jessen et al., 2014).

Generally, SCD has been perceived as a transitional stage between physiological ageing and MCI.

The original SCD criteria (Jessen et al., 2014) has been formulated as:

- Subjectively experienced and persistent cognitive decline compared to a previously perceived normal state, whereas this decline is unrelated to an acute disease
- Normal performance on standardized cognitive tests with respect to age, education and sex.

Therefore, the self-reported SCD in an older person should warrant further clinical evaluation. For one, to address non-neurodegenerative causes such as psychiatric condition, neurological disease, medication side effects, sleep disturbances or other systemic disease. For two, to ascertain an objective cognitive decline by neuropsychological testing.

A follow up visit should be scheduled when considering an individual with SCD in clinical practice, as it has been established that SCD is associated with an increased risk of AD (Mitchell et al., 2014) and an increased risk of abnormal (positive) AD-related biomarkers (Jessen et al., 2018; Sperling et al., 2011; van Harten et al., 2013; Wolfsgruber et al., 2017).

A meta-analysis of longitudinal studies (Mitchell et al., 2014) suggested that 14% of individuals with SCD declined to dementia in the future, and 27% declined to MCI in the future. Therefore, although in many individuals who concurrently report SCD, this is not associated with an objective cognitive decline, but it is associated with an increased risk of future cognitive decline. Prevalence studies estimated that 50% to 80% of elderly over 70 years old do report SCD at some point of their life (Jessen et al., 2010; van Harten et al., 2018). This is a high number, and it is currently not feasible or economical to clinically evaluate all elderly with concurrent SCD to justify the hypothesis that some of them will progress in the future. Secondly, the SCD is a very heterogeneous group in terms of underlying aetiology and thus heterogeneous in longitudinal trajectory and prognosis. Some SCD individuals revert to normal ageing, some remain stable with their SCD but no objective cognitive impairment, while a proportion goes on to developing objective impairment or dementia (Jessen et al., 2020).

Those SCDs who eventually progress and decline cognitively, are often those with abnormal AD-related biomarkers. Prospective studies on those who went on to develop dementia in the future suggested that it took approximately 10, perhaps 15 years, on average, to progress from SCD to dementia (Amieva et al., 2008; Verlinden et al., 2016). This is well aligned with several studies on temporal progression of AD-related biomarkers and the AD biomarker model derived by Clifford Jack (Jack & Holtzman, 2013; Jack, Knopman, et al., 2013; Jack, Knopman, et al., 2010). Thus, the time window between SCD complain and fully developed dementia is approximately 10 to 15 years which aligns with temporal evolution of AD biomarkers and provides an opportunity in for pharmacological and non-pharmacological interventions that are more effective early on. Similarly, this time window provides an opportunity for various prevention and secondary prevention strategies such as diet, physical activity, mental activity or treatment of modifiable risk factors and comorbidities.

While assessment of AD-related biomarkers in SCD individuals is very helpful in stratifying at-risk SCD subpopulation, at the time of writing of this thesis, it is still not feasible to administer AD biomarkers to large SCD populations in large campaigns. In potentially near future this might change, given the advent of biological therapies for AD and availability of blood biomarkers.

Thus, together with a high proportion of elderly who self-report SCD, there has been a practical need to stratify or parse out those with SCD who exhibit features that increase the risk of cognitive decline. Therefore, SCD plus features have been suggested and later refined as follows (Nicholas et al., 2017; Roehr et al., 2016; Snitz et al., 2018; Valech et al., 2015; Verfaillie et al., 2019; Wolfsgruber et al., 2016):

- Subjective decline in memory irrespective of performance in other cognitive domains
- Onset of SCD in the past five years
- Onset of SCD when 60+ years old
- Worry associated with SCD
- Seeking for a medical help
- Confirmation of cognitive decline by an observer
- Persistence over the time
- Perceiving own cognition to be worse than that of peers of similar age

1.2.2. Mild cognitive impairment

The term MCI is a heterogeneous group of individuals with objectively measurable cognitive impairment that does not reach an intensity leading to loss of self-sufficiency. It is perceived as the prodromal stage of dementia.

The criteria for MCI were first defined by Ron Petersen in 1999 (Petersen et al., 1999) and initially included solely patients with memory impairment (thus, amnestic MCI). However, criteria were later updated to include patients with other than memory impairment (thus, non-amnestic MCI).

MCI criteria by Petersen et al., 2004 (Petersen, 2004) are as follows:

- Cognitive impairment indicated by patients themselves or a proxy
- Cognitive impairment in one or more cognitive domains is disproportional with respect to patients' age
- ADLs remain preserved
- Dementia syndrome is not present

Impairment in one or more cognitive domains that is not proportional to patients' age, however, needs to be carefully interpreted as an expression of a change in the patient's condition. The decision whether this is a normal state or a cognitive deficit already is left to

the judgement of the physician. In clinical practice, however, neuropsychological testing is often utilized, and the patient's performance is compared to the normative established for a given age and education. The abnormal score is typically considered when performance drops below 1.5 SD, sometimes below 1.0 SD of a normative for a given age and education (Ivnik et al., 1999; Petersen, 2004).

MCI is a significant risk factor for dementia. Prevalence of MCI has been reported to be between 12-18 % of adults over 60 years old (Di Carlo et al., 2007; Petersen et al., 2010). AD is the most likely aetiology (Okello et al., 2009).Well-established findings from the longitudinal studies have shown that approximately 5 to 6 % (Roberts et al., 2012), some studies suggesting up to 12 % of MCI patients do progress to dementia annually (Busse, Angermeyer, et al., 2006; Busse, Hensel, et al., 2006). Cumulatively, a majority, although not all, MCI patients progress to dementia eventually. Proportion of MCI can remain stable, and some even regress/convert back to normal cognitive status or to SCD (Figure 5, above (Cheng et al., 2017; Liew, 2020). Reverse conversion may be due to fluctuations in cognitive performance or a non-neurodegenerative cause of MCI (e.g., depression) and more often described in population-based studies. Because an early diagnosis (predominantly speaking about AD) is of a high importance, identification of the factors that significantly increase the likelihood of conversion to the dementia is critical. Well-established factors of MCI to AD dementia conversion are hippocampal atrophy on MRI (Jack et al., 1998; Jack et al., 1999; Jack et al., 1997), reduced glucose metabolism in temporo-parietal regions (Pagani et al., 2015; Sperling et al., 2011), presence of abnormal deposits of Aß in cortex on Aß-PET, or presence of deleterious APOE ε4 allele (Iaccarino et al., 2017; Jack, Wiste, et al., 2010; Ma et al., 2014; Wolk et al., 2009) (Da et al., 2014; Elias-Sonnenschein et al., 2011; Xu et al., 2013), which has a dose-dependent effect (Herukka et al., 2007). Because of the availability of AD-related biomarkers, and availability of evidence supporting the relation ship between abnormal biomarkers and progression of the disease from MCI to overt AD dementia, MCI due to AD criteria were designated by Albert et al. (Albert et al., 2011).

Based on the cognitive profiling, MCI can be further classified into:

- amnestic MCI (aMCI), with dominant memory impairment as per definition, although impairment of other cognitive domains can be present as well;
- non-amnestic MCI (naMCI) with impairment of one or more non-memory cognitive domain, although memory impairment of certain degree is often present as well.

Following this arborization, MCI can be further subclassified into:

- single-domain MCI with one cognitive domain impaired;
- multi-domain MCI with several cognitive domains impaired.

This MCI classification has some practical implications in aiding the identification of those who may be more likely to progress to AD dementia versus other (neurodegenerative) dementias, even in the absence of established AD or other biomarkers. Amnestic MCI patients are more likely to progress to AD dementia (Oltra-Cucarella et al., 2018). Conversely, non-amnestic MCI individuals may be more likely to progress to DLB (Ferman et al., 2013) with relatively more prominent visuospatial impairment, FTLD with more affected behaviour, executive functions and language, or to vascular dementia.

1.2.3. Dementia

Dementia is a clinical syndrome not associated with just one specific aetiology.

Dementia syndrome is characterised by a progressive and often permanent cognitive deterioration that interferes with self-care and daily activities (ADLs), often rendering individuals dependent on others. At the dementia stage, there is a prominent neuronal and synaptic impairment and often a prominent neuronal loss on brain imaging (atrophy). The aetiologies underlying the dementia are multiple, ranging from a heterogeneous group of NDD to a multitude of systemic conditions (Figure 3).

In 2011, McKhann et al proposed (McKhann et al., 2011) updated criteria of dementia syndrome "all-cause" (without referring to a specific underlying aetiology) and criteria for dementia due to Alzheimer's disease.

Dementia is judged when cognitive and/or behavioural changes:

- hamper the ability to perform at work or in daily activities;
- indicate a decrease from a previous level of functioning;
- cannot be explained by delirium or other primary psychiatric disease.

Judgement of the cognitive impairment takes into account available information from patient's history, caregiver information and neuropsychological evaluation. At least two of the following should be present:

- decreased capacity to learn and recall new material;
- inability to analyse and solve more complex problems, "poor judgement";

- impairment in visual-spatial functions;
- impairment in language functions;
- deviations in conduct, personality, and demeanour

The two most common (neurodegenerative) aetiologies behind normal ageing-abnormal ageing-SCD-MCI-dementia continuum will be further discussed: Alzheimer's disease and Lewy body disease (dementia with Lewy bodies).

1.3. Alzheimer's disease

AD is the most common cause of the dementia syndrome, accounting for 55-70 % dementia cases, which translates to approximately 28-39 million of individuals with AD dementia worldwide. This number is projected to almost triple by 2050. Alzheimer's disease and dementia as such have been the fifth top cause of older adult mortality in western countries. In the Czech Republic, there are approximately 160.000 patients with dementia, most of them with AD or mixed AD-vascular which translates to approximately every 13th individual in the age category 65+, or every 5th individual in the age category 80+, and the females are twice as much affected as males (report of the Czech Alzheimer Society 2020).
Pathologically on microscopic level, AD is characterized by extracellular accumulation of diffuse Aß and more deleterious dense, fibrillar (neuritic) plaques and intracellular accumulation of neurofibrillary tau tangles (NFTs). On macroscopic level, the abnormal protein accumulation translates to the neuronal loss perceived as an atrophy on visual inspection. Biochemical and pathophysiological changes consistent with AD begin years to decades before the clinical symptoms are apparent (Villemagne, Burnham, Bourgeat, Brown, Ellis, Salvado, Szoeke, Macaulay, Martins, Maruff, Ames, Rowe, Masters, et al., 2013) (Jack, Knopman, et al., 2013), often with a window of 10-25 years which constitute the strategic opportunity to intervene (Sperling et al., 2011).
Clinically, the typical AD dementia is characterized by profound memory impairment and brain atrophy on MRI especially in MTL regions, which recapitulates the progression of AD-related neuropathology.

1.3.1 Neuropathology of AD

Based on the consistent findings from autopsy studies, it has been widely accepted that AD changes related to abnormal NFTs formation commence in the region of the entorhinal cortex in medial temporal lobe (MTL) and subsequently spread to hippocampus and other

limbic regions, then neocortical regions and later to most brain regions including brainstem in the most severe stages. One of the earliest regions affected are basal (cholinergic) forebrain structures, and some works even suggest this region may be affected at the very beginning (Schmitz et al., 2016). The sequence and topography of (the typical) AD pathology spreading across the brain has been operationalized using NFT pathological Braak stageing (Braak & Braak, 1991a; Braak et al., 2011) (Figure 6). On the other hand, Aß changes which preceed NFT pathology, progress in somewhat opposite direction to NFT changes: they appear in the basal neocortical regions and continue to all neocortex before spreading across the brain, operationalized in Thal stageing (for any plaques (Thal et al., 2002) and CERAD (for neuritic plaques) systems (Mirra et al., 1991) of autopsy amyloid stageing (Figure 6).

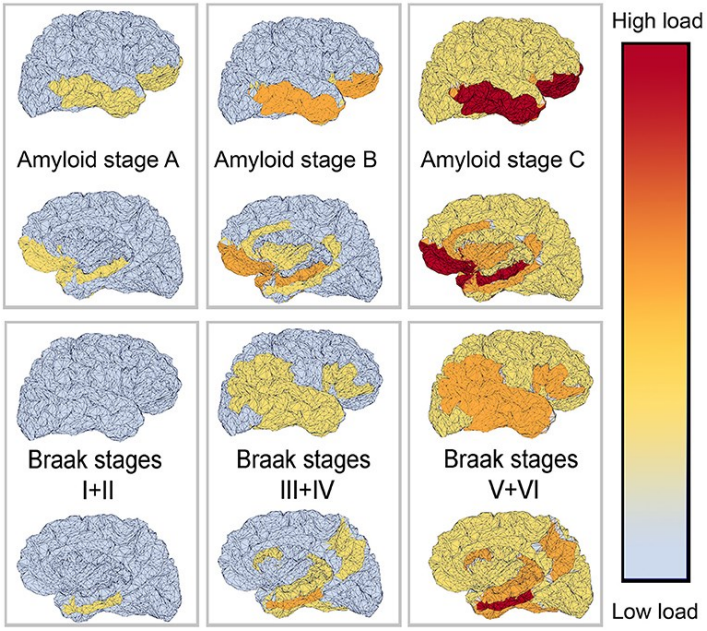


Figure 6. summarizes sequence and topography of abnormal neuritic amyloid plaques (top row, pathological stages A-C according to CERAD amyloid plaque stageing) and abnormal NFT formation using I-VI Braak stages (bottom row), adapted from (Stefanovski et al., 2021).

1.3.2. Amyloid or tau?

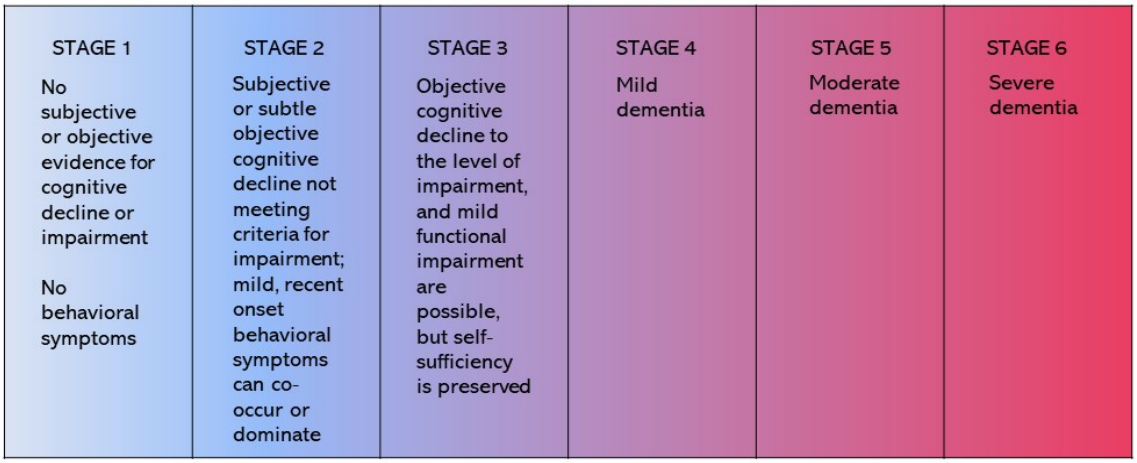
Amyloid protein has physiological roles in the synaptic plasticity and neuronal survival (Pearson & Peers, 2006), and limited concentrations of amyloid in brain are beneficial. **Amyloid hypothesis** (Selkoe & Hardy, 2016,Morris, 2014 #102) of AD stipulates, that the main culprit of AD are abnormal amyloid deposits resulting from abnormal metabolism and cleavage of amyloid precursor protein (APP) by secretase enzymes, consisting of various peptide and protein species forming diffuse and neurotic plaques, including oligomers that

are particularly neurotoxic (Kim et al., 2009). Amyloid, furthermore, triggers the accumulation of hyperphosphorylated tau protein into NFTs which is associated with the inflammation, oxidative stress, neuronal dysfunction, neuronal death, and the whole downstream deleterious cascade of events. Against this hypothesis some researchers argue using findings that Aß plaques are found in brains of cognitively normal individuals, and Aß plaques alone do not cause neurodegeneration (Morris et al., 2014). Some researchers suggest that amyloid is "an (innocent) bystander". However, current definitions of AD require both pathologies to be present, and hypothesize that AD is amyloid-ignited tauopathy. Conversely, the **tau hypothesis** stipulates that although tau protein also has physiological functions in microtubule structure and axonal transport (Avila et al., 2004), an abnormal tau species maturation and accumulation precedes Aβ plaque formation, and that phosphorylated tau aggregation into NFTs is the primary cause of neurodegeneration in AD. NFTs are found in brains of individuals with very mild dementia but no Aß pathology (de Paula et al., 2009), and NFT stageing correlates better with clinical progression of AD than Aß does (Braak & Braak, 1991b). Abnormal tau, in the absence of abnormal Aß, is also found in FTLD brains and other tauopathies. However, the pathophysiology of tau tangles is heterogeneous with several tau-species described, such as 3R (typical for FTLD), 3/4R (AD) or 4R (often associated with PSP or CBD).

Various other hypotheses such as prion-like, mitochondrial are others have been corroborated to answer what triggers the AD cascade. In conclusion, AD pathophysiology is very complex, and both Aß-related and tau-related factors are at play necessarily.

1.3.3. AD continuum and diagnosis

As discussed in detail in brain ageing section, AD develops within and across individuals in a continuum of clinico-pathologic changes from preclinical stage with positive AD biomarkers and potentially SCD, but formally unimpaired cognition and functioning, to prodromal stage with objective cognitive impairment but self-sufficient to fully blown dementia syndrome (*Figure 7. is self-explanatory, below*).



In order to aid both research-based and clinical setting-based diagnosis of individuals who are being evaluated for AD, various international working groups such as NIA-AA developed recommendations for the preclinical (Sperling et al., 2011), MCI (Albert et al., 2011), and the dementia stages (McKhann et al., 2011). In practice, AD diagnosis making includes thorough examinations: patient history taking, neuropsychological evaluation for cognitive profile, brain imaging for brain atrophy assessment and for differential diagnosis, laboratory tests to exclude other reasons and comorbidities, neurology examination and other available information. The diagnosis of early AD stages in particular relies on AD biomarkers more heavily.

1.3.4 AD biomarkers

A biomarker is a naturally occurring molecule, gene, or other characteristic by which a specific pathological process or disease can be identified. In AD, the traditional biomarkers such as cognitive or structural imaging have been conventionally used, although these are not specific to AD exclusively. In recent years, the specific biofluid-based and molecular imaging-based biomarkers have enabled in vivo identification of AD-related Aß and NFT tau changes. Biomarkers increase the diagnostic accuracy, monitor the disease progression, aid the differential diagnosis, and help to identify the participants who may benefit the most from the targeted treatments and interventions. The amyloid “A”, tau “T”, and neurodegeneration “N” have been the synonyms for AD and for biomarkers associated with AD having the practical implications for organization of AD-related clinical research.

1.3.4.1. Molecular AD biomarkers

Molecular or metabolic biomarkers are based on the presence of abnormal AD-related

proteins either in the CSF or in brain tissue itself scanned by PET using specific tau- and Aß-related tracers or glucose hypometabolism on FDG PET. These methods have now been well-established, standard in vivo biomarkers (Blennow & Zetterberg, 2018; Humpel, 2011; Klunk, 2011; Klunk et al., 2004; Palmqvist et al., 2015), however, they are relatively expensive. In recent years, thus, blood-based tests, e.g., single molecule array technology, have been developed and translated to clinical research, offering the hopes for a very convenient, minimally invasive, rapid and relatively cheap identification of at-risk individuals (Teunissen et al., 2022). However, in blood-based biomarkers field, more research is warranted to understand their correlation with well-established biomarkers, clinical disease progression, derive their respective specificities and sensitivities, and suggest technical and harmonization protocols to make blood-based methods more generalizable.

1.3.4.1.1. Aß in CSF

CSF Aß analytical methods are targeted the soluble forms of Aß species. The lower concentrations of $Aß_{42}$ in CSF reflect the increased accumulation of Aß in the brain. This CSF-based deviation from normative may be the first AD biomarker which is detectable not just several years before the onset of clinical symptoms, but when other established AD biomarkers are still within normal limits (Buchhave et al., 2012; Jack, Knopman, et al., 2013). Lower secretion of $Aß_{42}$ into the CSF translates into abnormal Aß accumulation displayed by amyloid PET. Reduced $Aß_{42}$ in CSF is suggested to predict amyloid PET positivity (Jack, Knopman, et al., 2013), although both CSF and PET methods correlate well with autopsy-derived findings (Palmqvist et al., 2015) and generally correspond well to each other. However, situations where CSF-based and PET-based amyloid measures are discordant are seen in practice and are problematic especially in early stages of the disease where diagnosis relies on biomarkers (de Wilde et al., 2019). Methodological differences and standardization, especially in CSF analytical procedures, can underlie these challenges (Hansson et al., 2018): there is heterogeneity across the centers in analytical methods and all centers have their own cut-offs for normal/abnormal biomarker score. Compared to a single Aß protein fraction (e.g., $Aß_{42}$ alone), the CSF $Aß_{42}/Aß_{40}$ ratio has been demonstrated as more sensitive, more specific (Schindler et al., 2019) and more robust, perhaps also due to the leveling of the interindividual differences. The downside of Aß biomarkers, both fluid-based and PET-based, is that they do not correlate well with cognitive impairment and disease progression.

1.3.4.1.2. CSF total tau and phosphorylated tau

The total tau (t-tau) levels correspond to the intensity of the neuronal damage and death in neurodegeneration. This is non-specific, however, and elevated t-tau levels are demonstrated in a multitude of other neurodegenerative and systemic or traumatic situations than AD alone (Blennow et al., 2001) such as other tauopathies, traumatic brain injury, ALS, Creutzfeldt-Jakob Disease or even stroke. For these reasons, the phosphorylated tau to t-tau ratio (p-tau/t-tau) has been used in AD diagnosis making since this ratio is higher in AD compared to other situations except for CJD, however, in CJD this ratio is by many orders of magnitude higher in CJD compared to AD.

The abnormal, p-tau in CSF of patients with AD also corresponds to the neuronal death. Similarly, to Aß, there are several strains of p-tau, such as p-tau 181 or p-tau 217, that are particularly useful in AD diagnosis. Unlike amyloid, p-tau proteins track with cognitive decline in AD. P-tau 181 correlates well with underlying neuropathology and longitudinal progression to AD dementia (Janelidze, Mattsson, et al., 2020), but it can be elevated in other tauopathies as well. Changes in CSF p-tau 181 are suggested to precede tau PET accumulation often (Ossenkoppele, Reimand, et al., 2021), which is important for AD biomarker temporal modelling and management of AD diagnosis in the early stages. However, p-tau 217 has demonstrated to perform better as an AD biomarker (Hanes et al., 2020; Janelidze, Stomrud, et al., 2020), including higher correlation with tau-PET and amyloid-PET accumulation and distinction from FTLD and other tauopathies. The most recent research suggests that the changes in another tau species, p-tau 231 in CSF are temporally preceding changes in other tau markers (Ashton et al., 2022). The limitations to p-tau biomarkers are similar as to all other CSF and blood-based biomarkers: preanalytical, storage, and analytical differences across sites, along with site-specific cut-offs that can cause diagnostic discrepancies in clinical setting and decrease the generalizability of findings in the research-based setting.

1.3.4.1.3. Aß PET imaging

Aß PET is a nuclear medicine technique employing specific radioligands for the *in vivo* detection and visualization of Aß-related pathology. Together with CSF AD-related pathology analysis, the significance of PET imaging increases in clinical diagnosis, differential diagnosis and especially with the advent of clinical trials targeted at abnormal proteins. The first Aß tracer was developed at the University of Pittsburgh, the carbon-11

labelled Pittsburgh compound B (PiB; (Klunk et al., 2004), a well-established biomarker of Aβ *in vivo* which correlated well with underlying Aβ pathology at autopsy (Ikonomovic et al., 2008; Reiman et al., 2009; Sojkova et al., 2011). However, the disadvantage of PiB tracer has been the short half-time about 20 minutes which is impractical and requires an on-site cyclotron. Subsequently, multiple other ligands have become available, most often incorporating radiolabelled fluorine-18 such as florbetapir, fluorbetaben and flutemetamol, with the latter two available in the Czech Republic during recent years. All ligands trace the fibrillar (neuritic) Aß density in the cortex but do not track well with toxic Aß oligomers that are too short. Unlike PiB, these fluorine-18 tracers have much longer half-times by order of hours, allowing for transportation of ligands to centers without a cyclotron. This has boosted incorporation of PET imaging especially in the clinical setting and clinical research. In the Czech Republic, Aß PET is covered in full by standard health insurance but due to a high price, it is tightly regulated by the national authority for drug control. For clinical purposes, the visual assessment of PET scan resulting in the judgement of "negative" versus "positive" has been feasible and clinically useful, with both sensitivity and specificity ranging between very decent 88 to 92% compared to autopsy (Rowe et al., 2013; Salloway et al., 2017; Thurfjell et al., 2014). Aß PET in clinical setting has been very valuable to perform differential diagnosis of the atypical clinical presentations such as primary progressive aphasia (PPA) which is often associated with AD pathology but other neurodegenerations have been associated with PPA as well.

For research purposes, however, quantitative methods of amyloid detection have been more suitable and preferrable to address. The standardized uptake value (SUV) or SUV ratio (SUVR) comparing Aß retention in several cortical regions combined against Aß retention in a reference region, typically in cerebellum. Like CSF Aß-based biomarkers, amyloid PET positivity vs negativity requires a cut off value that can be object to a certain fluidity based on an experience of the center, their hypothesis etc. Therefore, harmonization procedures are necessary too. The efforts resulted in so-called the Centiloid scale to standardise the results of Aß PET (Klunk et al., 2015) .

Although there is a dynamic in Aß deposition in brain over time which can be detected by longitudinal PET scanning, and Aß PET certainly does predict conversion to more advanced stages in the AD continuum, the major disadvantage of this method has been that PET findings do not correlate well with the disease progression. Some studies suggested associations of amyloid with worse performance on various cognitive tests, but the findings have been equivocal. Another caveat is that as much as 20-30% of cognitively unimpaired

older persons have abnormal (positive) amyloid PET(Jack et al., 2014; Jansen et al., 2015), although not all of them would progress to clinically apparent AD. Thus, other strategies need to identify those who are at highest risk of clinical decline.

My research into the prediction of at risk of AD individuals is presented in Clinical research part of this dissertation, Study IV. under Aim 2 (Nedelska et al., 2017).

On the other hand, Aß PET methods have been useful in the imaging of Aß co-pathology in other diseases as well such as DLB (Burack et al., 2010; Kantarci, Yang, et al., 2012), and is negative in other tauopathies such as some FTLD syndromes that can be mistaken for AD (Drzezga et al., 2008).

The **"A" acronym** from ATN criteria that are corroborated below stands for amyloid-related CSF and PET imaging biomarkers of AD pathology in vivo.

1.3.4.1.4. Tau PET imaging

Like Aß PET methods, tau PET utilises specific radioligands to detect abnormal tau protein accumulation *in vivo*. This includes heterogeneous spectrum where AD is the most frequent. Other tauopathies include PSP, Pick's disease (behavioural variant of FTD), CBD, Down's syndrome, or non-fluent/agrammatic variant of PPA (Grossman, 2010a, 2010b), or situations when AD is an overlapping pathology, such as DLB or PDD (Leuzy et al., 2019). The tau tracers are targeted at the paired helical filaments in NFTs that are typical for AD whereas other tauopathies are typically associated with other tau species. There are several tau tracers from the first generation and the more advanced second generation of tracers with improved pharmacokinetics and less off-site binding are available, however, mostly for research purposes. In the Czech Republic, the approval of PET tracer is pending (Leuzy et al., 2019; Okamura et al., 2018).

The major advantage of tau PET is that that it visually traces the magnitude and the topography or localization of tangles in a brain *in vivo and* corresponds very well to NFT Braak stageing at autopsy (Adams et al., 2019; Maass et al., 2017; Schwarz et al., 2016). Moreover, tau PET, unlike Aß PET, tracks well with cognitive decline and disease progression (Okamura et al., 2014; Ossenkoppele, Smith, et al., 2021) and has a potential in clinical trials both for patient selection and as a surrogate measure of outcome. The ability of tau PET to predict cognitive performance has been demonstrated to be superior to that of volumetric MRI and Aß PET (Jack et al., 2019; Ossenkoppele, Smith, et al., 2021). Moreover, whereas up to 20-30% of cognitively unimpaired adults have positive amyloid

PET, and amyloid alone is not a good predictor of cognitive decline, abnormal tau PET even in the absence of amyloid is associated with abnormal cognition much more frequently. Adults demonstrating both abnormal amyloid and tau-PET although clinically unimpaired are very likely to progress to AD dementia within 3-5 years (Ossenkoppele et al., 2022).

The disadvantage of tau PET is the high cost and the off-site binding of the tau tracers (Baker et al., 2019; Lemoine et al., 2018). This stems from the partial overlap of tau-tracers targeted to helical tau filaments which also partially bind to other tau species in no-AD tauopathies and atypical regions such as substantia nigra in PSP or PDD (Lowe et al., 2016; Marquie, Normandin, et al., 2017; Marquie, Verwer, et al., 2017) or to monoamine oxidase B in basal ganglia. The second generation of tau tracers, however, have improved in off-target bindings.

The **"T" acronym** from ATN criteria stands for tau-related CSF (specifically p–tau) and PET imaging biomarkers of AD pathology in vivo.

1.3.4.1.5. FDG PET imaging

18 radiolabelled fluorine deoxy-d-glucose (FDG) PET is molecular imaging method that measures brain glucose metabolism which is primarily driven by the synaptic activity and basal processes such as maintaining the ion gradients, resting and task-independent activity. Because brain utilizes the glucose as one of its major fuels, this tracer with 110 minute half-time is particularly suitable to measure the brain metabolism. Impaired glucose metabolism on FDG PET is a result of a complex cascade involved in AD pathogenesis that can be labelled as neurodegeneration: including the expression of certain genes, oxidative stress, mitochondrial impairment, decreased plasticity, glial activation and inflammation, synaptic loss and neuronal death. The **"N" acronym** stands for neurodegeneration in vivo in ATN criteria. The signature pattern of glucose hypometabolism on FDG PET in AD patients involves the precuneus in the medial parietal cortex, the posterior cingulate, the inferior parietal lobe, lateral temporal cortices, and the medial temporal lobe, especially the hippocampus (Minoshima et al., 1994; Minoshima et al., 1997; Reiman et al., 1996). The disease-specific patterns of FDG hypometabolism have shown a 96% accuracy to discriminate cognitively normal, 94% FTLD, 92 % DLB and 95% AD (Mosconi et al., 2008). The magnitude of hypometabolism on FDG PET tracks with the disease progression (Lo et al., 2011). Further, FDG PET hypometabolism correlates well with tau-related AD biomarkers (Petrie et al., 2009). Moreover, there is a very good correlation between the region of hypometabolism and clinical manifestation (such as degree of semantic memory

impairment and MTL hypometabolism), although this is aetiology non-specific.

The disadvantage of FDG PET is relatively high cost and limited availability associated with manufacturing and lower half-time of FDG. Moreover, the FDG hypometabolism is nonspecific in terms of the underlying cause including stroke or neuroinflammation. This method has been uncommon in clinical or research setting in NDD in the Czech Republic.

1.3.5. Model of AD biomarkers and practical operational framework

Based on extensive findings from the imaging-clinical and cognitive association studies and clinico-pathologic studies involving participants from the AD continuum, the efforts were made to propose a model of AD biomarkers serving as a framework for *in vivo* AD staging (Jack, Knopman, et al., 2013 and operationalized into A/T/N scheme in 2018).

The model has focused on the most established AD biomarkers:

- "A" measure of Aß accumulation, that is CSF $A\beta_{42}$ and Aß PET imaging
- "T" measures of tau accumulation, that is CSF p-tau and tau PET
- "N" measures of the quantitative or topographic biomarker of neurodegeneration or neuronal injury, that is CSF t-tau, glucose hypometabolism on FDG PET and atrophy on structural MRI

Amyloid biomarkers, specifically CSF-derived $A\beta_{42}$, become abnormal first, followed abnormal amyloid PET, followed by CSF p-tau, then tau PET, followed by abnormal FDG PET and MRI. Cognitive impairment and the self-sufficiency impairment are the last steps in the AD progression cascade. This model for "pure" AD has become known as Jack's curves (Jack, 2022; Jack, Knopman, et al., 2013). This model may have a different shape and order in mixed or atypical presentations.

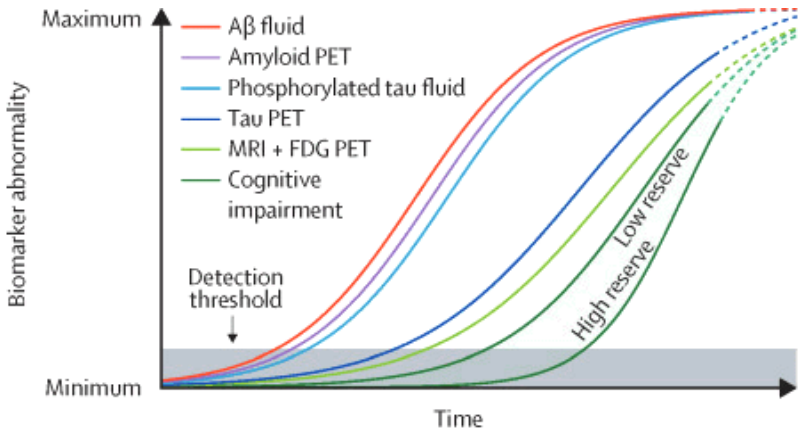


Figure 8. Model of the biomarker dynamic in the pathophysiology of AD, adapted from (Jack, 2022; Jack, Knopman, et al., 2013).

From this model it is obvious that biomarker curves are not linear over the time, but they have sigmoid shapes with respect to time, suggesting that earlier in the process, the rate of change of a given biomarker is higher but later the rate slows down and reaches a "plateau". This is important for planning of the clinical research and clinical trials. Further, the left part of the model concerns the earliest stages, including cognitive normal adults (or those with SCD) with abnormal biomarkers, transitioning to MCI as more and more biomarkers become abnormal, and then to dementia. This model suggests those often mentioned 10-15 years when biomarkers are abnormal already before the first clinical symptoms, usually identified at SCD stage, start to emerge. The pharmacological strategies, modification of the risk factors, nonpharmacologic interventions such as diets, physical and mental wellbeing strategies are more likely to be successful when applied in this window.

The A/T/N framework (Jack et al., 2018) was proposed as a guideline to research-based diagnosis of AD to find a "common language" across research studies communicating the AD biomarkers to increase the generalizability and head-to-head comparisons of study findings. The A/T/N framework can be applied to any neurodegenerative disease and can serve to rate AD when considered as a co-pathology. The framework also serves to communicate biomarker profiles at level of an individual person. The biomarker categories are labelled with + to denote the positive (abnormal) or – to denote the negative (normal) biomarker:

- A-T-(N)- denotes normal AD biomarkers
- A+T-(N)- denotes Alzheimer's pathologic change in AD continuum
- A+T+(N)- denotes AD in AD continuum
- A+T+(N)+ denotes AD in AD continuum
- A+T-(N)+ denotes Alzheimer's and suspected non-Alzheimer's pathologic change (SNAP) in AD continuum
- A-T+(N)- denotes non-AD pathologic change
- A-T-(N)+ denotes non-AD pathologic change (e.g., hippocampal sclerosis)
- A-T+(N)+ denotes non-AD pathologic change (e.g., PART or LATE)

This framework accepts that many details of AD pathogenesis are still uncertain, and that the various units exist which can clinically mimic AD but fail to demonstrate expected AD biomarker positivity: e.g., the limbic predominant age-related TDP-43 encephalopathy (LATE) with clinical amnestic syndrome, hippocampal atrophy on MRI, elevated tau in CSF

but negative amyloid biomarkers, or primary age-related tauopathy (PART)(Crary et al., 2014; Jack, 2014). These are pathology and biomarker-based units which can cause diagnostic challenges and their progression remains to be understood. Thus, this A/T/N framework can identify the units that are not captured by any diagnostic systems such as NIA-AA. For example, A+T-N+ can denote the earliest preclinical AD (A+T-) with overlapping hippocampal sclerosis (N+) prognosis of which is uncertain.

The prerequisite for this A/T/N system is the definition of biomarker cut-offs for abnormality vs normality. As discussed earlier, this a weak point of translating biomarkers to clinical practice and object of a high methodologic heterogeneity. Cut-offs and methodological differences create the grey zones when the biomarker status is uncertain, and the biomarker is uninformative for potential clinical diagnosis making.

In summary, the main idea behind A/T/N framework has been primarily for research purposes to be able to organize clinical trials in preclinical or early symptomatic individuals, however with the recent success of biological treatment of AD it will very likely transit into the clinical practise. ATN criteria recognize AD as a biological entity and neglect clinical phenotype of the patients which is the main difference to all previous diagnostic criteria.

1.4. Conventional and advanced MRI methods

In recent decades, there has been a major shift from structural imaging being the tool to exclude other, potentially treatable conditions such as tumour, stroke of normal pressure hydrocephalus to the central role of structural imaging as tool to diagnose specific neurodegeneration along with other diagnostic modalities, to monitor the disease progression or to use structural imaging as surrogate measure of outcome in clinical trials.

1.4.1. Structural MRI

Brain atrophy is a visualization of neurodegeneration. Atrophy measured from T1-weightedMRI volumetry correlates with neuronal counts at autopsy (Bobinski et al., 1999; Gosche et al., 2002; Jack et al., 2002). Atrophy of hippocampus and medial temporal lobe structures on MRI is a signature pattern of typical AD (de Leon et al., 1989; Jack et al., 2002). It has been used as MRI signature region both in clinical qualitative readings for AD and in quantitative volumetric methods used more for research purposes. Distribution and magnitude of atrophy on MRI correlates with severity of cognitive impairment in both cross-sectional and longitudinal AD imaging studies (Fox, Scahill, et al., 1999; Fox, Warrington,

et al., 1999; Hua et al., 2008; Jack et al., 2002). MRI atrophy recapitulates well the Braak staging, showing entorhinal cortical atrophy and basal forebrain atrophy in early clinical stages through whole brain atrophy in fully blown AD dementia. MTL atrophy in MCI individuals predict progression to AD dementia although when used alone, it does not have high specificity or sensitivity – between 50 to 70% (DeCarli et al., 2007). Similarly, a focal atrophy shown on MRI correlates with specific cognitive domain impairment such as worse memory performance on AVLT correlates with hippocampal atrophy, but this correlation is rather aetiology non-specific. Despite this, medial temporal atrophy MRI atrophy is routinely used in differential diagnosis both in clinics and in research: in AD, MTL atrophy is more pronounced than in DLB, when not considering cases with overlapping pathologies, or in vascular dementia. Conversely, MTL atrophy can be more severe in FTLD subtypes such as semantic variant of PPA compared to typical AD.

In general, MRI has been very well-established method in clinical setting due to its wide availability, affordability, non-invasivity, a high tolerability by patients, and utilization in multiple medical specialties which warrants the continuous technological development of MRI methods. In the clinical setting, to aid visual interpretation of MRI based atrophy on the level of an individual patient, several visual scales have been implemented for regional or whole brain atrophy. For example, Pasquier's global cortical atrophy (GCA(Pasquier et al., 1996)) visual scale has been designed to visually evaluate cortical atrophy on whole brain level across normal ageing and various NDD in the differential diagnosis. Koedam scale (Koedam et al., 2011) has been devised to visually inspect parietal cortical regions that are typically atrophied in PCA. Scheltens MTL atrophy visual scale (Scheltens et al., 1997; Scheltens et al., 1992), Kipps-Davies frontal atrophy visual scale has been devised originally for FTLD to visually evaluate frontal cortical regions (Davies et al., 2006; Kipps et al., 2007) or Fazekas scale for white matter hyperintensities related to small vessel disease from FLAIR MRI images (Wahlund et al., 2001). All these semiquantitative scales operate typically on 0 to 3 or 4 grades with higher grades indicate more severe atrophy or white matter impairment. They offer cost-effective, convenient, and rapid diagnostic tools for clinical practice. Because the regional atrophy itself is aetiology non-specific, the visual scales have been criticized for low specificity and sensitivity but combining scores from visual rating across different brain regions can increase their diagnostic value (Harper et al., 2015). Unlike quantitative volumetric methods, visual scales do not require specific software, hardware, or expertise, and can be adopted by any professional after some routine practice.

Autopsy studies, later recapitulated by structural MRI studies identified patterns of atrophy

that are associated with typical NFT and amyloid pathology at autopsy in both typical and less typical localizations compared to **typical "amnestic" AD**. These **atypical AD subtypes** account for up to 30% of AD cases (Murray et al., 2011): **limbic predominant** type with profound MTL atrophy similar to hippocampal sclerosis but minimal atrophy in other regions – the subtype observed in the oldest old or **hippocampal sparing** subtype with minimal MTL atrophy but profound atrophy in parietal and frontal cortices, sometimes labelled as **dysexecutive AD** seen generally in younger patients than in those with typical AD atrophy pattern. This seminal autopsy study has been recapitulated by in vivo structural MRI study with quantitative volumetry (Whitwell et al., 2012). Furthermore, implementing various MRI visual atrophy scales also yielded clinically distinct subtypes of AD (Ferreira et al., 2017), similar to autopsy and quantitative volumetric studies. Additionally, the MRI study with visual rating scales (Ferreira et al., 2017) identified fourth atrophy pattern subtype, **minimal atrophy** which, together with hippocampal sparing subtype showed less aggressive disease progression.

1.4.2. Diffusion MRI

Diffusion tensor imaging (DTI) is not as conventional technique in AD evaluation because it requires more advanced technical background and computation. However, DTI provides different flavour of anatomical information. By utilizing the anisotropic nature of water molecules diffusion which is impeded perpendicular to white matter (WM) fibres, DTI provides information on the microstructural integrity of WM and grey matter. The disruption of natural microstructural barriers to free water diffusion such as myelin sheaths, cell membranes or intracellular components results in measurable differences in water diffusion. Fractional anisotropy (FA) has been a robust DTI measure that lessens proportionally to WM degeneration (Pierpaoli & Basser, 1996). Thus, FA has been used as a proxy of WM integrity (Carmichael & Lockhart, 2012; Douaud et al., 2011). Higher FA corresponds to higher density of white matter tracts or compartmentalization of WM. Another metrics, mean diffusivity (MD) evaluates all-directional water movement, and is inversely proportional to FA. MD has been more useful to investigate microstructural integrity of brain cortex compared to FA. These two DTI measures have demonstrated changes in early presymptomatic AD and progression from MCI to AD dementia (Nir et al., 2013; Oishi et al., 2011, 2012). Higher MD and lower FA in regions typical for AD such as entorhinal cortex, cingulum and precuneus showed correlations with NFT Braak stageing and with clinical disease severity in AD patients (Kantarci, Murray, et al., 2017). A method of

automated fiber quantification provides a different angle of view to study white matter impairment using DTI during the early stages of AD (Zhang et al., 2019).

1.4.3. Arterial spin labelling

ASL is an advanced MRI (Detre et al., 2009; Williams et al., 1992) technique for quantifying brain tissue regional cerebral blood flow by using water molecules in the blood as endogenous magnetically labelled tracers. The major advantage is that ASL can be included in a routine MRI scan and does not require the injection of a radiotracer or contrast agent unlike FDG PET. It has a potential to substitute FDG PET, since the hypothesis is that glucose metabolism and blood perfusion are two closely coupled processes (Madsen et al., 1995). However, it has not been widely used technique despite its affordability, accessibility and non-invasivity likely due to the technical implementation and image processing requirements. ASL MRI comprises several acquisition techniques (Musiek et al., 2012; Wolk & Detre, 2012), e.g. the pseudo-continuous ASL (Dai et al., 2008) which has demonstrated very good reliability and precision compared to the gold standard perfusion ^{15}O-water PET in individuals with AD dementia (Xu et al., 2010).

1.4.4. Proton MR spectroscopy

^{1}H-MRS resonance spectroscopy allows for the quantification of multiple brain tissue metabolites simultaneously in a single MRI examination. H-MRS can be sampled from multiple brain voxels or a single voxel. Single voxel H-MRS is typically acquired from a posterior cingulate which has been associated with early changes in AD. Whereas creatine levels have been stable in various pathological processes and have been used as internal reference in H-MRS studies, other metabolites have corresponded to differential aspects of cellular and molecular pathophysiological processes. N-acetyl-aspartate (NAA) is predominantly found in neuronal bodies and axons and has been used as a marker of neuronal density and viability. Decreased NAA level has been demonstrated both in WM and grey matter of AD patients and correlated with NFT tau pathology. Further, myo-inositol (mI) is predominantly found in glia, and its elevated levels correspond to the glial proliferation and inflammation (Glanville et al., 1989). Decreased NAA and increased mI levels have been consistent findings in AD patients compared to normal elderly (Huang et al., 2001; Meyerhoff et al., 1994; Pfefferbaum et al., 1999). In clinically unimpaired older individuals at risk of developing AD, the elevated mI has corresponded to lower CSF Aß$_{42}$ levels, a

higher Aß accumulation on PET and higher Aß load (Voevodskaya et al., 2016) in autopsy-confirmed study (Murray et al., 2014). Furthermore, an increased mI level has been demonstrated in cognitively normal APOE ε4 carriers with negative amyloid PET (Voevodskaya et al., 2016). This is aligned with findings that APOE ε4 may enhance the glial activation and modify the association between glial activation and Aß accumulation. However, more research on the relationship between H-MRS and its significance to amyloid biomarkers is needed. This is corroborated under Aim 2, Study IV by (Nedelska et al., 2017).

1.5. Cognitive AD biomarkers

1.5.1. Conventional episodic memory-based tests

Conventionally, the diagnosis of AD has relied significantly on demonstrating cognitive deficits using the traditional neuropsychological testing, especially tests of episodic memory. Episodic memory is associated with the time dimension of information, and with adequate processing by the hippocampus. Thus, impairment of the episodic memory is associated with hippocampal atrophy. Both episodic memory (Park & Reuter-Lorenz, 2009) and MTL decrease during the course of normal ageing are not sufficiently aetiology-specific, i.e. both memory and MTL decrease in other neurodegenerations, for example svPPA (Hodges & Graham, 2001), bvFTD (Hornberger et al., 2010) or PART (Teylan et al., 2020). During AD, episodic memory impairment, and the corresponding hippocampal atrophy tracks with autopsy NFT Braak III to IV stage which in turn corresponds to MCI syndrome. Therefore, episodic memory tests alone are not sufficient for early AD diagnosis. Memory testing can be obscured by language impairment and is limited by the ceiling effects, and conversely, can be compensated for by a higher educational or occupational attainment. Moreover, whereas episodic tests are sensitive to hippocampal atrophy, conventional neuropsychology tests in general have not been optimally sensitive to basal forebrain or entorhinal cortex impairment which are affected by AD pathophysiology early on. Traditional paper and pencil-based neuropsychology tests have cross-cultural disparities and do not enable comparisons between animal versus human cognitive performance which has been used as primary and secondary outcome measure in drug trials. Studies performed by our group in cohorts recruited in the Czech Republic and by other groups internationally have repeatedly demonstrated that spatial navigation, although of an experimental rather than well-established nature, may be a cognitive skill that is affected very early during the AD.

1.5.2. Experimental cognitive tests: spatial navigation

Although the traditional neuropsychology tests are standardized , they are language- and also culture-dependent and somewhat static tests. However, cognitive impairment in AD extends beyond paper-and-pencil to more complex sensory, emotional and social cognition impairment.

Spatial navigation is a process that enables organisms and humans a purposeful movement around the environment and to determine the route from one location to another. Thus, spatial navigation is a critical skills needed for every-day functioning. The accurate spatial navigation results from a complex information processing including visual, auditory, somatosensory, vestibular and prorioceptive information (Bates & Wolbers, 2014). Hence, a network of brain structures (Chen, Qing, et al., 2021; Li et al., 2021) and pathways are associated with spatial navigation. Spatial navigation performance changes during the normal ageing (Cerman et al., 2018; Gazova et al., 2012), but is significatly impaired in the AD early on (Allison et al., 2016; Coughlan et al., 2018; Lithfous et al., 2013; Mokrisova et al., 2016). Thus, having the better understanding of the processes associated with the spatial navigation impairment in early AD stages, as well as the tools to measure these processes and specific brain structures involved in spatial navigation, could assist the development of more accurate language – and culture-independent tests (Laczo et al., 2012b) for detecting the early AD stages. Although the spatial navigation is complex, two most fundamental spatial navigation strategies have been outlined: 1. **Egocentric or body-centered** spatial navigation which utilises the position of the individual's own body and bodily axes (e.g., up-down, left-right, backward-forward) in the environment as a frame of reference for determining a route to a destination. This strategy is primarily associated with the posterior parietal cortex, precuneus and nucleus caudatus (deIpolyi et al., 2007; Igloi et al., 2010; Weniger et al., 2011). 2. **Allocentric or world-centered** spatial navigation which utilises the relative positions of places and objects to other objects (landmarks) to plan a route through the environment.During this process, a cognitive map is created as an iternal image of the environment, landmarks and the destination. This strategy is independent of one individual's position, and is associated with the hippocampus (Maguire et al., 1998) in particular, the enorhinal and parahippocampal cortex (Ekstrom et al., 2003) but is also associated with structures outside the MTL such as basal forebrain, thalamus, and prefrontal cortices (Chen, Wu, et al., 2021; Kerbler et al., 2015; Lerch et al., 2022; Moffat et al., 2007; Qing et al., 2017). The allocentric strategy is severely impaired in both the MCI and dementia stages of AD as well as in preclinical AD (Allison et al., 2016; Hort et al., 2007; Laczo et

al., 2009; Parizkova et al., 2018; Wu et al., 2016). Egocentric strategy is also impaired in patients with MCI due to AD and AD dementia (Allison et al., 2016; Hort et al., 2007 (Laczo et al., 2022), but likely this impairment follow the allocentric impairment. The human analogue of the Morris water maze (hMWM) has been designed to examine spatial navigation in humans; hMWM has since been validated and used as a tool for assessing spatial navigation at different stages of AD.

1.5.3. Social cognition and emotional recognition

Neuropsychiatric symptoms may manifest frequently and early during the course of AD. These symptoms have a strong correlation with both patient quality of life and caregiver distress (Mukherjee et al., 2017). Moreover, neuropsychiatric symptoms are regarded as one of the most important factor associated with the probability of institutionalisation (Schoenmakers et al., 2009). Research findings suggest that neuropsychiatric symptoms may stem from social cognition deficits. It encompasses several processess, including the interpretation of emotional cues communicated by others e.g., facial expression recognition, empathy, and moral processes, e.g. prosocial behavior. Particularly, the impaired recognition of others' emotions is associated with neuropsychiatric symptoms (Santamaria-Garcia et al., 2020).

Emotional recognition comprises a complex of behaviours involving perception social judgement, interoception, and expressions (Adolphs et al., 2002). An accurate emotional processing and recognition is vital to communication encompassing a variety of modalities, including gestures, facial expressions, voice, and prosody which are the acoustic properties of speech, e.g. the rhytm, melody, tone, volume. Impaired emotional recognition affects the quality of social interactions, relationships and life. Emotional recogniton was demonstrated to be impaired in patients with MCI due to AD and AD dementia (Elferink et al., 2015). Previous studies suggested that emotional recognition has been associated with temporal structures, especially right-sided, such as amygdala (Gallagher & Chiba, 1996), anterior cingulate cortex (Bush et al., 2000) and temporal pole (Olson et al., 2007), therefore regions which are also associated with AD. Social cognition is becoming one of the hot topics of the current AD research, but more research is warranted to offer more accurate tests and strategies to modify and enhance social cognition in AD and other neurodegenerations.

1.6. Genetic markers: Apolipoprotein E

One of the most important risk factors in patients with late onset AD (the vast majority of

AD cases) is considered to be the presence of the ε4 allele of the APOE (Mahley et al., 2006). APOE ε4 carriership is associated with an increased Aβ accumulation in the brain (Fleisher et al., 2013), and different APOE alleles likely regulate this accumulation differentially (Verghese et al., 2013). APOE ε4 carriership is associated with worse cognitive performance and with accelerated brain atrophy, including the hippocampus. In the brain, APOE is expressed predominantly in the astrocytes, but can be produced by almost any cell. One of the functions of APOE is transport of the cholesterol and other lipid molecules from astrocytes to the neurons where the cholesterol is critical for the axonal and synaptic growth and remodelling. However, apolipoprotein E protein, is expressed in various parts of the body other than the brain and its physiology and pathophysiology remains to be understood in detail. Studies have shown that heterozygous carriers of the ε4 allele have approximately 3 times higher risk of developing AD and the quite rare homozygous ε4 who constitute are approximately 2% of the population have 12 to 15 times higher risk compared to homozygotes carrying the ε3 allele. Lifetime estimates of the development of AD in APOE ε4 homozygotes is up to 60%. Conversely, the presence of the ε2 allele has been demonstrated by some research groups as protective (Blennow et al., 2006). The deleterious effects of APOE ε4 are emerging also from the studies on other neurodegenerative dementias, such as DLB, e.g., through accelerating the concomitant AD-related pathology but also amyloid non-dependent mechanisms.

1.7. Therapies for AD

Currently, only symptomatic treatment for AD is widely available in clinical practice represented by the acetylcholinesterase inhibitors (AChEI; donepezil, rivastigmine and galantamine) and memantine. These long-time established agents are covered by patients' health insurance and showed to decelerate the clinical disease progression (Mohs et al., 2001) and delay in functional worsening (Winblad et al., 2006) in randomized double blinded trials. AChEI have been used in the treatment of the PDD and DLB patients (Rolinski et al., 2012), although formally, the DLB patients still need to be labelled as having a variant of AD to receive the treatment covered by the health insurance.

The tremendous efforts have been put into the development of disease modifying drugs that could effectively halt the disease course and improve cognition and functioning by modification of the biomarkers associated with the disease progression. Various approaches have been tried, and the mainstream have been anti-Aβ, anti-tau, neuroprotective agents, anti-neuroinflammatory, insulin resistance management and brain stimulation. In the anti-

Aβ category, the trials with monoclonal antibodies targeting the aggregation of Aβ have led to a controversial approval of aducanumab as treatment for AD in June 2021 in the United States, but this drug was not approved in the European Union. For now, several ongoing phase 3 trials have shown some promise in moderate slowing of Aβ accumulation, among which lecanemab (van Dyck et al., 2023), a humanized IgG1 monoclonal antibody that selectively binds to Aβ soluble protofibrils, showed reduced markers of Aβ in early AD and showed moderately less functional and cognitive decline compared to placebo, and was approved in the United States in January 2023.

1.8. Dementia with Lewy bodies

DLB is a clinical syndrome characterized by a presence of cognitive impairment (dementia) and (some) features of:

- spontaneous parkinsonism,
- (recurrent) visual hallucinations,
- REM sleep behavior disorder,
- fluctuations in cognition and alertness,
- and a range of other symptoms, e.g. dysautonomous or neuropsychiatric.

All symptoms or features can have a variable magnitude and frequency. In DLB, a cognitive decline should precede features of parkinsonims by at least 1 year (McKeith et al., 2017) which has been an useful rule in differentiating DLB from Parkinson disease dementia (PDD) where the motor impairment established as PD precedes cognitive impairment.

DLB is the second most common neurodegenerative dementia after AD (Zaccai et al., 2005), although in terms of frequency at memory clinics, such as our clinic in Prague, the FTLD spectrum competes for the second place. The prevalence studies have reported a wide range of proportions of DLB patients (Vann Jones & O'Brien, 2014), with a mean prevalence of 7.5 % in clinic-based studies. These are, likely, underestimated values because DLB has been one of the most misdiagnosed dementias (Nelson et al., 2010) as autopsy studies have reported 16-24% prevalence of dementia associated with Lewy bodies.

Whereas AD is more common in women, DLB is more common in men.

1.8.1. Neuropathology of DLB and importance of overlapping pathologies

DLB is pathologically defined by underlying Lewy body disease (LBD). Together with

Parkinson disease (PD) and multiple system atrophy (MSA), these belong under the umbrella of LBD. LBDs are characterized by intracellular aggregations of α-synuclein (Spillantini et al., 1997) called Lewy bodies (Kosaka, 1978) and Lewy neurites in neuronal cells and axons in DLB and PD and in oligodendrocytes (MSA) which leads to neurodegeneration. Like tau and Aß in AD, α-synuclein has a physiological role in synaptic transport and modulation but undergoes abnormal misfolding under certain conditions that are less understood in DLB than in AD. Abnormal accumulation of α-synuclein is also a pathologic feature of pure autonomic failure (PAF) and idiopathic REM sleep behavior disorder (RBD). RBD is gaining more and more acceptance as a prodromal stage of "traditional" α-synucleinopathies, DLB, PD and MSA.

However, the pathological landscape of DLB is considerably more complex; AD-related pathology, Aβ plaques and NFT-tau, do frequently overlap with LBD (Hamilton, 2000 Schneider et al., 2007).The degree of overlapping AD pathology on the top of LBD is variable, from minimal to severe, including highest Braak stages of NFT-tau. Ascertaining the AD-related pathophysiology in DLB is important because:

- Overlapping AD pathology can obscure typical DLB-related clinical features (Ferreira et al., 2020) and makes premortem diagnosis challenging. This applies especially to DLB patients with high degrees of parallel AD pathology, who are often clinically diagnosed as having AD (Merdes et al., 2003).
- DLB is one of the most misdiagnosed dementias (Nelson et al., 2010).
- DLB patients with mixed pathologies are more sensitive to neuroleptics (McKeith, 2004) and respond very well to AChEI (Graff-Radford et al., 2012)
- Mixed DLB patients clinically progress faster, cognitively decline faster (Rongve et al., 2016), are independent shorter (Rongve et al., 2014) and survive shorter (Lemstra et al., 2017) than DLB without AD co-pathology.

A recent meta-analysis of longitudinal studies concluded that DLB patients progress faster and survive shorter than AD patients (Mueller et al., 2019).

During the autopsy assessment, the likelihood that the pathologic findings are associated with a clinical syndrome of DLB is ascertained. The LBD is rated in a standardized brain sections and categorized as amygdala predominant, brainstem-predominant, limbic (transitional) or diffuse (neocortical). Simultaneously, the NIA-AA guidelines are applied to ascertain AD from the standardized brain sections. The less AD-related pathology is present, the more likely is clinical dementia syndrome associated with LB, especially cortical Lewy

bodies (*Table 2*)(McKeith et al., 2017).

Table 2. The likelihood that pathology is associated with clinical DLB syndrome.

AD neuropathologic change	NIA-AA none/low (Braak stage 0-II)	NIA-AA intermediate (Braak stage III-IV)	NIA-AA high (Braak stage V-VI)
Lewy body pathology			
Diffuse neocortical	**High**	**High**	**Intermediate**
Limbic (transitional)	**High**	**Intermediate**	Low
Brain-stem predominant	Low	Low	Low
Amygdala-predominant	Low	Low	Low
Olfactory bulb only	Low	Low	Low

As demonstrated, the clinical and pathologic landscape of DLB is quite complex and diverse. The *box 1* below summarized the basic terminology within the field.

Box 1. Basic terminology associated with the DLB field.

- **Dementia with Lewy bodies (DLB)**: dementia is present before or simultaneously with parkinsonism OR within 1 year of parkinsonism onset.
  * CAVE – not every DLB patient develops parkinsonism*
- **Parkinson disease dementia (PDD):** dementia develops 1 year or later after diagnosis of Parkinson disease is made
- **Lewy body dementias:** DLB and PDD
- **MCI-PD**: mild cognitive impairment in those with PD
- **Lewy body disease (LBD):** disease defined pathologically, autopsy diagnosis when the magnitude and spatial distribution of pathology is counted
- **RBD:** REM sleep behavior disorder
- **Prodromal DLB or MCI-LB**: novel research-based concept at the stage of MCI with typical DLB features. Some also accept RBD as prodromal DLB.

1.8.2. Clinical diagnosis of DLB

The course of DLB can be quite variable among the individual patients, owing to the frequently overlapping pathologies, to the fact that, unlike AD, LBD affects not just brain, but the periphery and autonomous system as well, and involves multiple mediator systems of the brain and body. The involvement of various mediator systems (*Figure 9, below*) is mirrored by variety of symptoms including cognitive, motor, sleep, autonomous, psychiatric etc.

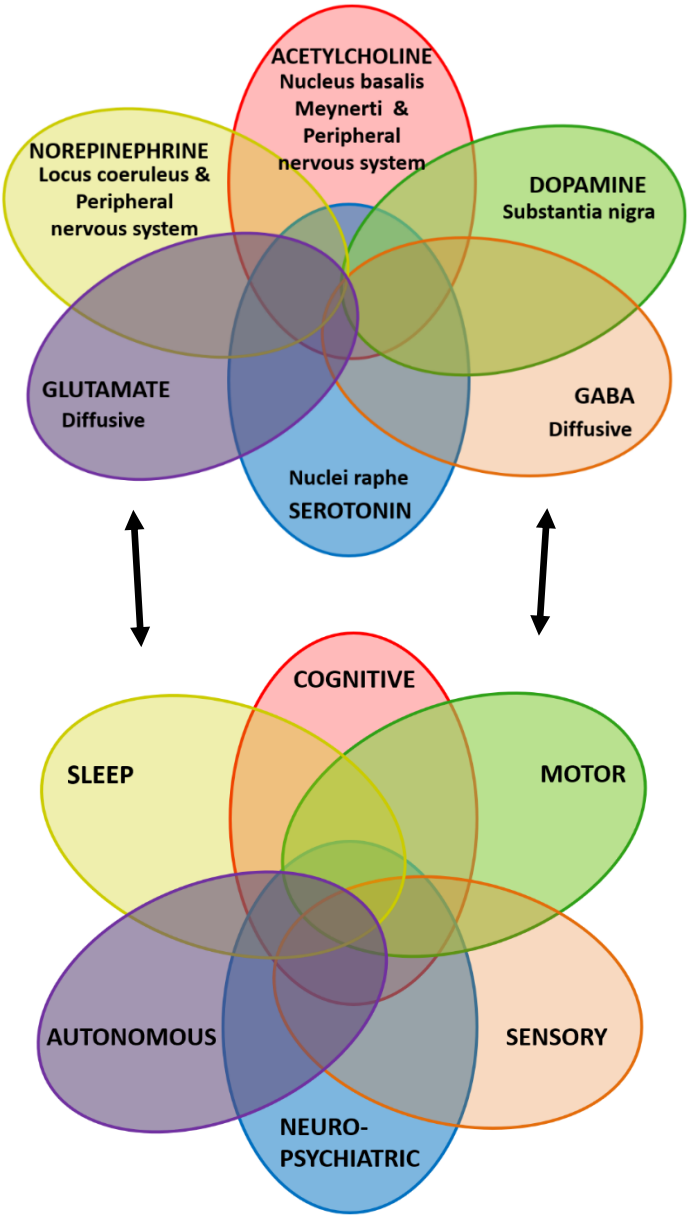


Figure 9. The mirroring of multi-mediator system impairment in diversity of clinical symptoms.

Because of this variability in DLB, the diagnostic ability of clinicians used to be low. To

improve the diagnostic sensitivity and specificity, the DLB Consortium led by Ian McKeith has prepared and then repeatedly revised the criteria for clinical and pathologic diagnosis of DLB, over and over again incorporating the new information about the core features and updating the recommended methods.

The 2017 report of the fourth DLB Consortium clearly distinguishes between the clinical features and diagnostic biomarkers, giving more diagnostic weight to RBD among the features, and to the ^{123}iodine-metaiodbenzylguanidine (MIBG) myocardial SPECT among the biomarkers, as more evidence accumulates to support the importance of these findings. The 2017 criteria weigh the probability of DLB as dementia aetiology in a given patient, and suggest two categories of clinically **probable and possible DLB.** The *Table 3* graphically summarizes the *core and supportive clinical features* and *indicative and Supportive biomarkers* used to make a diagnosis.

Table 3. Possible and probable DLB diagnosis by the 4th DLB consortium 2017

	Central	Core clinical	Supportive clinical	Indicative biomarker	Supportive biomarker
	Dementia as progressive **cognitive decline** with **impaired activities** of **daily living**	**Visual hallucinations** **Parkinsonism** **Fluctuating cognition** **RBD**	**Sensitivity to neuroleptics** **Autonomous dysfunction** **Falls** **Hyposmia** **Psychiatric symptoms**	**PSG** REM sleep behavior disorder **DAT-scan** Reduced dopamine uptake in basal ganglia **MIBG-scan** Myocardial reduced uptake	**MRI or CT** Preserved medial temporal lobe **FDG-PET** CIS sign Reduced occipital metabolism **EEG** Posterior Slow wave activity
Diagnosis					
Probable DLB	yes	≥ 2 feature			
Probable DLB	yes	1 feature		≥ 1 biomarker	
Possible DLB	yes	1 feature			
Possible DLB	yes	0		≥ 1 biomarker	

Based on 4th DLB consortium 2017 criteria, DLB is **less likely:**

- When other brain or physical illness is present that can account for the clinical impairment, such as cerebrovascular disease. However, these do not exclude DLB

diagnosis and can indicate mixed pathologies and causes of the clinical impairment.

- When parkinsonism is the only present core feature and appears at the severe dementia stage for the first time.

1.8.2.1. DLB core clinical features

Spontaneous parkinsonian features: are common in DLB, eventually developing in approximately 85% DLB patients. However, many DLB patients do not fulfill a parkinsonism typical for PD (bradykinesia with resting tremor and/or rigidity). In DLB, one of the typical parkinsonian features is requested. It should be distinguished from other comorbidities such as arthrosis or cognitive impairment that hampers motor evaluation etc. If in doubt whether symptoms are parkinsonian or not, a DaT scan may be helpful.

UPDRS scale including UPDRS motor subscale are used to examine these features.

Visual hallucinations (VH): should be complex visual hallucinations of a recurrent nature. VH occur in approximately 80% DLB patients at some point, often during the early stages. VH tend to be well-formed, depicting other people or invaders, insect, rodents, or other animals, sometimes along with sense of presence, illusions, sense of passage. Patients often have at least some insights into VH, as well as caregivers. The scales to assess VH are available.

Fluctuations: are spontaneous alterations of attention, arousal or cognition and can resemble delirium. They include inconsistent behaviours which can come and go, staring or zoning out, incoherence of speech and variable attention. The positive answers to questions such as daytime drowsiness, starring into empty space or lethargy are helpful. The scales to assess the frequency or severity of fluctuations are available. Because fluctuations can occur in other dementias, typically vascular or mixed, at later stages, they can be helpful especially in early stages of DLB.

REM sleep behaviour disorder (RBD): RBD is a parasomnia associated with the loss of normal REM sleep atonia. It includes dream enactment behaviour; patients are 'acting out' their dreams; move, toss, kick, shout to mimic their dreams. The typical dreams include motives of chasing, attacks etc. Patients can inflict injuries to themselves or their partners.

RBD especially is gaining an attention in LBD field because it often manifests many years to decades before other features become apparent and can wane over time. RBD should be distinguished from RBD mimics such as periodic limb movements, obstructive sleep apnoea, or episodes of confusion on waking up etc. If in doubt whether symptoms are RBD or not,

polysomnography (PSG) is needed.

RBD was not the DLB core clinical feature before, but its inclusion improves the diagnostic accuracy of DLB (Ferman et al., 2011) since 76% of DLB patients who are autopsied have RBD whereas less than 4% of autopsied non-DLB patients have RBD. When dementia and RBD are added into a model evaluating the probability of DLB, the specificity increases to 90%. Conversely, majority of patients with idiopathic RBD followed up longitudinally develop features of DLB, PD or MSA (Iranzo et al., 2014) and majority of these have α-synucleinopathy at autopsy (Lu et al., 2013). Thus, the evidence that RBD is a very early, prodromal stage of DLB (or PDD) is increasing (Postuma et al., 2019). However, not all DLB patients have RBD, and absence of RBD does not exclude DLB diagnosis. The assessment scales and questionnaires targeted at RDB ascertainment are available.

1.8.2.2. Supportive DLB clinical features

These include high sensitivity to (atypical) antipsychotics, falls, postural instability, autonomic dysfunction (e.g., orthostatic hypotension, constipations, erectile dysfunction, urinary incontinence), syncope, hyposmia, hypersomnia, apathy, depression, anxiety, pseudo-hallucinations, or hallucinations in other than visual domains. All of these are common and often early, but do not have a higher diagnostic specificity. However, they are useful in DLB diagnosis especially if they persist over the time or if several of them co-occurs.

1.8.3. DLB biomarkers

Unfortunately, unlike the AD field, the direct in vivo biomarkers of LB pathology or α-synucleinopathy are not yet available, there are several modalities that can be used as indirect biomarkers. In the 2017 fourth DLB Consortium criteria, the biomarkers are operationalized as **indicative** or **supportive**.

1.8.3.1. DaT scan: indicative biomarker

The DaT radionuclide (^{123}I-ioflupane) along with PET or SPECT is used to demonstrate the reduced postsynaptic dopamine transporter uptake in basal ganglia. DaT scan has demonstrated its value in distinguishing DLB from AD (specificity 90 and sensitivity 78%)(McKeith et al., 2007). Typically, the signal is more reduced, thus abnormal, in caudate, appearing on the DaT scan as full stop (DLB) compared to normal coma-like shape in AD

and controls (*Figure 10*). Thus, if we have patient with dementia, one core DLB feature and abnormal DaT scan, we can make the diagnosis of probable DLB. However, DaT scan alone cannot reliably distinguish between DLB and PD/PDD or atypical parkinsonism such as PSP or MSA, CBD or some FTLD, and other clinical evaluations should be used to do so. Some DLB patients without parkinsonism and/or minimal substantia nigra loss and brainstem atrophy at autopsy

can show normal DaT scan, or the DaT scan finding may be atypical but not fully abnormal as expected for DLB. In some cases, DaT scan can be normal (negative) on a scan performed early during the disease but can become abnormal (positive) later as disease develops (van der Zande et al., 2016), and rescanning should be considered especially if only 1 core feature is present and can make a difference by assigning a correct DLB diagnosis.

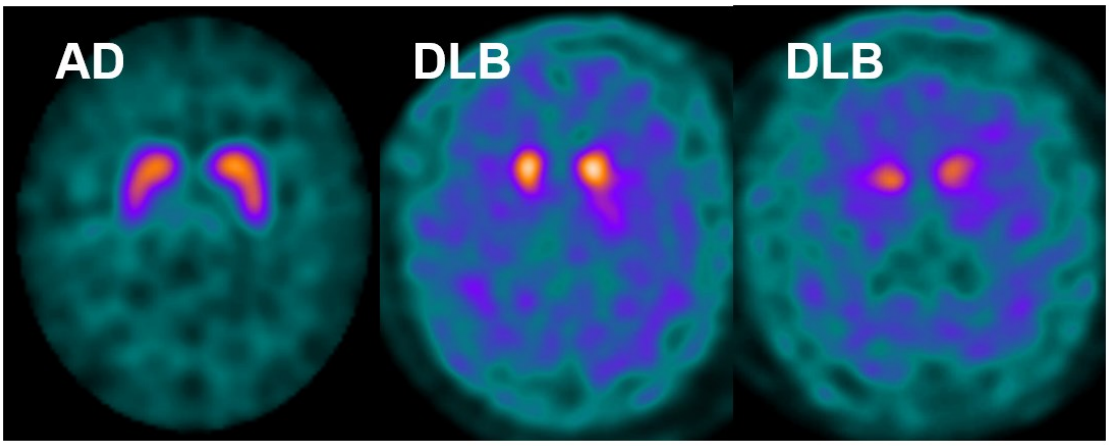


Figure 10. DaT scans of an AD patient (left), showing the normal DAT uptake in putamen and caudate bilaterally (coma-like shape). An abnormal DaT scan showing reduced uptake in caudate or both putamen and caudate bilaterally (full-stop shape) in two different DLB patients (middle and right). Courtesy of Dr. Zuzana Nedelska

1.8.3.2. MIBG scan: indicative biomarker

The reduced uptake on ^{123}I-metaiodbenzylguanidine myocardial SPECT showing an impaired postganglionic sympathetic innervation in the heart muscle scaled by mediastinum (heart-to-mediastinum ratio) is a finding indicative of LB already at earlier stages. Patients with RBD or MCI with Lewy body core features often have abnormal (reduced) MIBG scan. The sensitivity and specificity of distinguishing between AD vs DLB has been 70% and 90% when using an automated software or 69% and 87% on visual assessment, but the specificity increased to 94% in milder DLB cases (Yoshita et al., 2015). MIBG scan can further help

also in the differential diagnosis of Parkinson plus syndromes. However, there are confounding factors to be considered when reading MIBG scan such as various medications, ischemic heart disease, peripheral neuropathies, heart failure, diabetes etc.

1.8.3.3. Polysomnography: indicative biomarker

PSG is a method of choice to confirm the suspicion on a RBD without atonia. RBD without atonia is highly specific predictor of LB pathophysiology (Boeve et al., 2013). A patient having dementia and a positive history of RBD, followed by a PSG examination that confirms RBD without atonia, can have a diagnosis of probable DLB assigned.

1.8.3.4. Relative preservation of medial temporal lobe structures on MRI: supportive biomarker

The following biomarkers show findings consistent with DLB and are useful in the clinical evaluation and clinical research. However, they do not possess a higher diagnostic specificity, and categorized as *supportive*.

Both clinically diagnosed and autopsy-confirmed cohorts of AD patients show greater atrophy in the hippocampus and amygdala (Barber et al., 2000; Burton et al., 2004; Kantarci, Ferman, et al., 2012) and also rates of atrophy in hippocampus and amygdala on longitudinal measurements (Nedelska, Ferman, et al., 2015; Whitwell et al., 2007). Thus, observing minimal MTL atrophy on MRI is typical for (pure) DLB but would not be typical for AD where MTL atrophy is one of the hallmarks. However, seeing a profound MTL atrophy in DLB patients is not exclusive of DLB diagnosis but rather suggest an overlapping pathology (most likely AD). Profound MTL atrophy on MRI in DLB patients is suggestive of more aggressive disease, and faster disease progression. This is more researched by Nedelska et al., 2015 under Aim 3., Study V. (Nedelska, Ferman, et al., 2015).

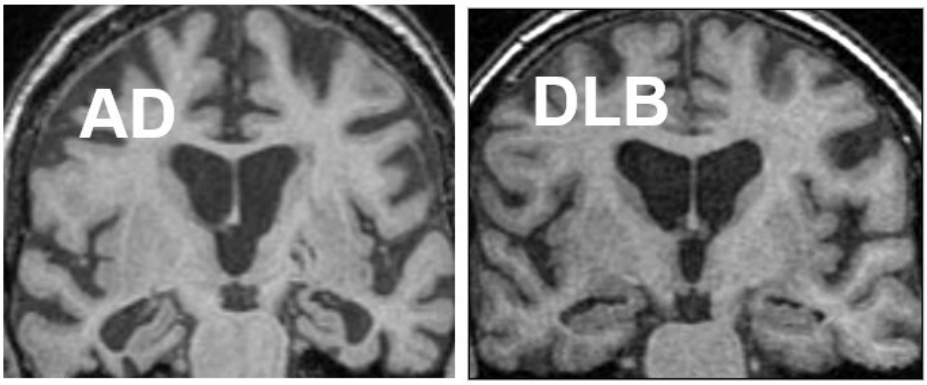


Figure 11. These coronal views of T-weighted MRI scans show comparison between a marked atrophy in the whole brain and especially in MTL in an AD patient (left) who is of the same age and same global cognitive status than DLB patient (right) with less pronounced atrophy and relatively spared MTL. Courtesy of Dr. Zuzana Nedelska

1.8.3.5. Reduced occipital glucose metabolism and cingulate island sign on FDG-PET: supportive biomarker

DLB patients show parieto-occipital cortical hypometabolism on FDG-PET (Imamura et al., 1997; Kantarci, Lowe, et al., 2012; Minoshima et al., 2001) whereas typical AD patients have occipital metabolism preserved. Occipital hypometabolism in DLB patients correlates with neuropathology of visual cortex (Higuchi et al., 2000). However, patients with atypical AD such as those with posterior cortical atrophy (PCA) syndrome with atypical distribution of AD-related pathology, may be problematic though as they may also show occipital hypometabolism and some other features similar to those with DLB. Thus, occipital hypometabolism is not enough specific, and is only supportive biomarker.

The metabolic pattern specific to DLB is so-called **cingulate island sign (CIS).** CIS is visually preserved metabolism in posterior cingulate cortex relative to the hypometabolism in precuneus and cuneus (*Figure 12*)(Imamura et al., 1997; Lim et al., 2009). Because in AD, posterior cingulate gyrus, and also cuneus and precuneus show one of the earliest metabolic defects (Reiman et al., 1996), related to AD pathology, patients with AD do not show the CIS.

The quantitative ratio comparing metabolism in posterior cingulate divided by metabolism in cuneus and precuneus combined, is CIS ratio, and may be potentially used in clinical studies. Both, CIS and CIS ratio are sensitive measure of overlapping AD-pathology in DLB patients. The more AD pathology (especially NFT-tau), the less visible CIS is and CIS ratio diminishes (Graff-Radford et al., 2014; Nedelska et al., 2018) (Nedelska et al., 2019), corroborated in detail by Nedelska et al., 2019 and under Aim 3., study VII by Nedelska et

al., 2018 and by a supportive study to this dissertation on tau-PET accumulation and clinical presentation in DLB patients by Nedelska et al., 2019 (Nedelska et al., 2019).

Because the blood perfusion of the brain tissue is tightly coupled with brain glucose metabolism, MRI-derived perfusion method ASL could be potentially used when FDG-PET is not available. More research on this is performed in Aim 3, Study VII by Nedelska et al., 2018.

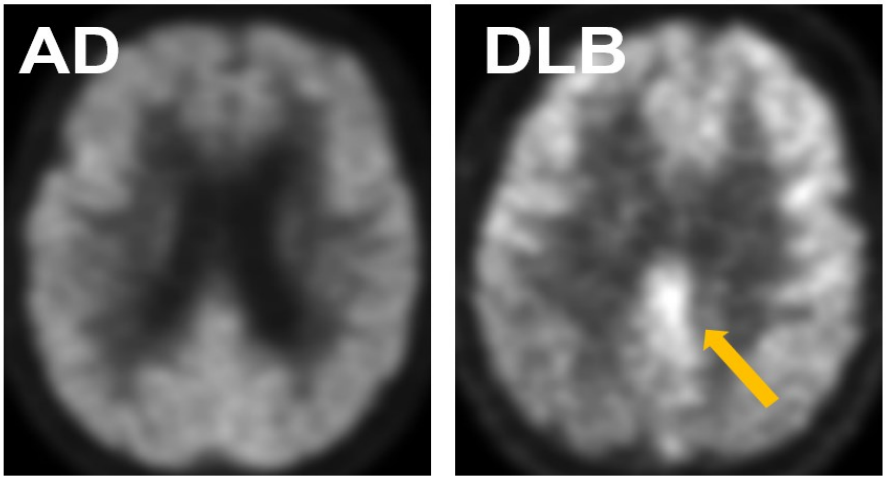


Figure 12. The FDG-PET scans show axial view of cortical glucose metabolism in a typical AD patient (left) who has both lateral and temporal hypometabolism including posterior cingulate cortex, cuneus, and precuneus, thus no CIS is visible. On the other hand, a DLB patient (right) has occipital metabolism, but metabolism in posterior cingulate is relatively spared compared to hypometabolism in cuneus and precuneus. Hence, the CIS (yellow arrow) is visible. Courtesy of Dr. Zuzana Nedelska.

1.8.3.6. Posterior slow wave activity on EEG with periodic fluctuations – supportive biomarker

Increasing number of studies demonstrate EEG abnormalities in posterior regions showing either stable (pre)alpha-dominant frequency or mixed with alpha, delta and theta in certain patterns (Bonanni et al., 2008). These EEG abnormalities correlate with severity of cognitive fluctuations and are observed as early as in patients with MCI and Lewy body features (Bonanni et al., 2015). Recent studies demonstrated predictive value of over 90% in distinguishing DLB from AD using these EEG patterns (Bonanni et al., 2016).

1.8.3.7. Molecular imaging of overlapping AD-related pathology in DLB

Amyloid and tau-PET using the same tracers that are used in patients with suspected AD-

related pathology have been used in DLB patients to ascertain the degree of overlapping pathologies in DLB. Overlapping AD pathology in DLB patients is associated with a faster clinical and cognitive decline and a shorter survival rate, to assess mixed AD pathology in DLB is important for prognosis making. Moreover, with the advent of biologic therapies targeted at AD, the DLB patients with higher degrees of AD pathology may benefit from these treatments in the future as well.

More than a half to two thirds of DLB patients do show significant levels of PiB accumulation on PiB amyloid PET (Petrou et al., 2015). The distribution, or the pattern, of amyloid tracers in DLB is similar to the diffuse distribution of amyloid tracers seen in AD patients. In terms of tau-related accumulation on PET, clinically probable DLB patients have shown significantly lower tau-tracer uptake than AD patients. Unlike amyloid PET, tau-PET also has a region-specific binding, showing significantly less tau-PET accumulation in the medial temporal regions in DLB which completely distinguishes them from patients with AD dementia (Kantarci, Lowe, et al., 2017). More on the tau-accumulation on DLB is researched by Nedelska et al., 2019 (Nedelska et al., 2019) in a supportive study to this dissertation. On the other hand, DLB patients do show some “atypical” tau-binding in posterior parietal and occipital cortices compared to controls. Amyloid PET accumulation correlates with tau PET accumulation in DLB patients, supporting these methods as visualization of in vivo AD pathology in DLB.

The first and only longitudinal study on amyloid accumulation and relationship to longitudinal clinical decline in DLB patients is presented under Aim 3., study VIII by Nedelska et al. 2019.

Findings on amyloid- and tau-related biomarkers derived from CSF and PET and their relationship to clinical phenotype in a multinational DLB cohort is presented in a by Ferreira et al., 2020 and by Abdelnour et al, 2020 - studies supportive to this dissertation (Abdelnour et al., 2020; Ferreira et al., 2020)

Based on the knowledge accumulated from longitudinal and autopsy-confirmed studies in patients with DLB, similar model introducing the temporal ordering of AD biomarkers by Cliff Jack (Jack & Holtzman, 2013), could be derived for DLB patients (Walker et al., 2015) (Fields et al., 2011)(*Figure 13*).

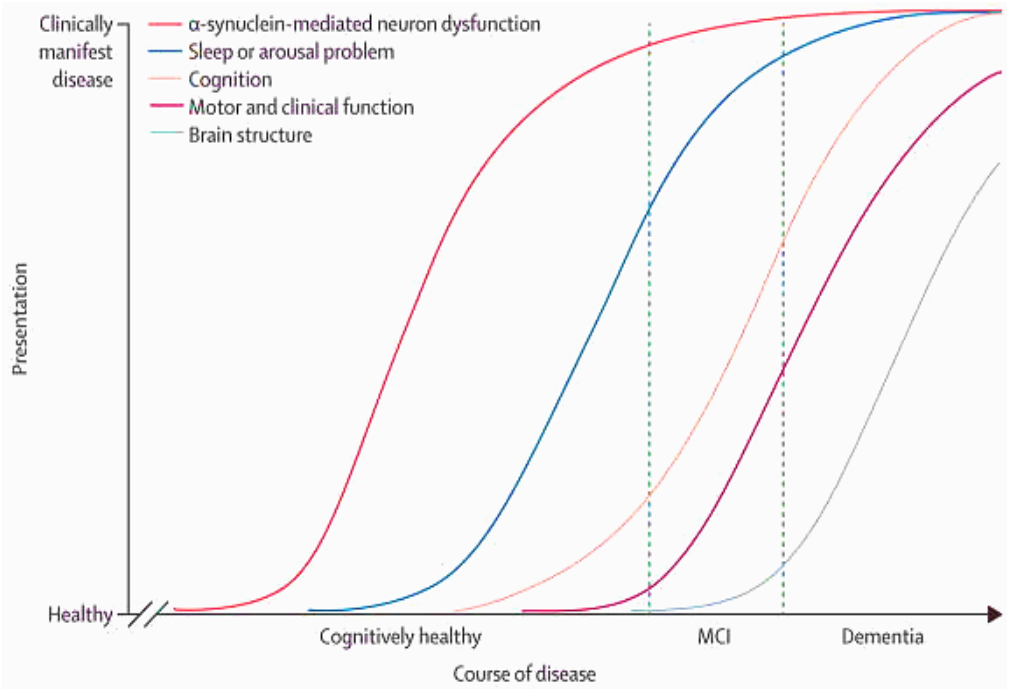


Figure 13 adopted from Fields et al 2011 and Walker et al 2015 shows the proposed model of the temporal evolution of DLB biomarkers: the neuronal dysfunction mediated by α-synuclein is manifested first as a sleep-related or arousal problem (RBD), followed by cognitive impairment, then motor and other clinical symptoms, and brain structure eventually (Fields et al., 2011; Walker et al., 2015).

1.8.4. Genetic markers in DLB

Similar to sporadic AD dementia, APOE ε4 allele is overrepresented in DLB patients (Bras et al., 2014; Rongve et al., 2019; Tsuang et al., 2005), and is a strong risk factor across the LBD spectrum. APOE ε4 frequency increases from PDD to DLB. Because ε4 allele has been associated with a higher likelihood of "pure" synucleinopathy in autopsied patients with minimal AD-related pathology, the APOE ε4 might act through a different mechanism that amyloid-related in DLB and synucleinopathies (Tsuang et al., 2013). On the other hand, higher frequency of APOE ε4 has been associated with higher degrees of AD-related pathology in DLB patients.

Variant alleles for glucocerebrosidase beta (GBA) have been other major sporadic genetic risk factor for DLB (Rongve et al., 2019).

1.8.5. Clinical management and therapy of DLB

Because the symptoms in DLB, and the underlying pathophysiology is so complex and variable, including the involvement of multiple mediator systems, and organs across the body and brain, the clinical management is also a complex process. Diagnosis making includes multimodality evaluations, because the symptoms can wax and wane, diagnosis making can take some time as the disease develops. Because the range of symptoms is included from cognitive through sleep, motor, sensor, autonomous, psychiatric etc, the treatment, which is solely symptomatic, is targeted at all these symptoms as they occur. The side effects can be problematic to balance as some antiparkinsonian drugs can worsen psychiatric or cognitive symptoms and vice versa.

For cognitive symptoms and also overall functioning and daily activities rivastigmine and donepezil have been used (Stinton et al., 2015; Wang et al., 2015). Beneficial effects of AChEI on visual hallucinations and RBD have also been reported in the research and clinical community.

1.8.6. DLB continuum and future directions

Similar to well accepted AD continuum of preclinical to prodromal to full blown dementia stages, the DLB also exists in a similar continuum although less research and knowledge is available for the earliest stages of DLB. In 2020, the research criteria for diagnosis of prodromal DLB have been formulated, and the research is warranted in prodromal DLB (McKeith et al., 2020).

More on MRI imaging in prodromal DLB is researched in Aim 3., study IX. by Kantarci and Nedelska, et al., 2022 (Kantarci et al., 2022). The research into cerebrovascular disease in DLB by Ferreira and Nedelska, et al., 2021 (Ferreira et al., 2021) is presented under Aim 3, study X.

Ascertaining various common risk factors such as sex differences, age, education, APOE and their relevance to the DLB pathophysiology and clinical phenotype is another direction of concurrent research (Oltra et al., 2023).

2. Aims and hypotheses.

2.1. My involvement and contribution to this research

During the work on the thesis and my postgraduate study spanning 12 years between 2010 and 2022 including personal and administrative breaks and foreign fellowships, I was involved in multimodality evaluation of patients, implementation of imaging protocols, participant recruitment and management, spatial navigation testing, data mining, comprehensive research administration and research conduct. I was a neurology resident in a training since 2010, seeing the patients from the general neurology field, including those with neurodegenerative diseases and especially those with AD. At the same time, I started my PhD studies in Neuroscience at the Memory Clinic, Department of Neurology, The Second Faculty of Medicine, Charles University and Motol University Hospital, where human spatial navigation clinical research has been the signature method. Ihave been examining patients, especially those with AD, and volunteers using spatial navigation tests. The cohort of patients later developed into longitudinal observational study on ageing and dementia, the Czech Brain Ageing Study.

I became responsible for magnetic resonance imaging and image analysis in our team and transitioned into imaging field. I applied the high-resolution MRI protocols that could be used for a quantitative analysis such as volumetry or morphometry since late 2011. These protocols are appropriate for quantitative analysis using automated algorithms such as FreeSurfer. I started to perform quantitative analysis of regional brain. Within our CBAS study, I applied the imaging protocols to Brno site of CBAS.

I have been lecturing at the University of the third age at the Second Faculty of Medicine, Charles University, which has also been one of the sources I started to recruit the cognitively unimpaired volunteers as controls for the CBAS projects since 2014.

As part of my PhD studies, I took a research fellowship and a senior research fellowship with the Division of neuroradiology, Department of radiology, Mayo Clinic Rochester, the Mayo Clinic Study of Ageing and Mayo Clinic Alzheimer's Disease Research Center. During my fellowships at Mayo Clinic, I advanced my expertise in multimodality imaging of dementia with Lewy bodies and Alzheimer's. I have been organizing all my projects and studies, from selecting the appropriate participants, performing data and image quality control, performing imaging analyses, organizing statistical analysis with help from departmental statisticians and epidemiologists, interpreting results, writing papers, and presenting at conferences. I analysed multimodality imaging from various MRI and tau and ß-amyloid PET methods in a setting of one of the largest research groups with high volume

and multisite data expertise. My domain were longitudinal observational studies which have different methodological considerations and approach compared to cross-sectional studies, especially in such field as is neuroimaging of ageing brains. I took a three-year postgraduate Master of Science program at Mayo Clinic in clinical and translational research including courses on study design, clinical trials, statistics, ethics and epidemiology and others.

In Prague, I became very involved in dementia with Lewy bodies cohort, evaluating and manageing patients clinically, as well as manageing research projects and testing new potential biomarkers in this field. I take care of research administration from institutional review board, ethics committee, dealing with GDPR, legal department and deputy of our hospital for research and science. I also regularly see patients with AD and other neurodegenerative aetiologies as a specialist in neurology.

The overarching purpose of my dissertation thesis has been to contribute to the timely diagnosis of AD and DLB, incorporating experimental neuropsychology tests and multimodality imaging methods that are available to research and health care professionals in the field of neurology, gerontology, and radiology. The potential general application of my findings is in the differential diagnosis, prognostication, selecting the participants who could benefit the most from targeted interventions, and evidence for using imaging as surrogate outcome measures in clinical trials.

Because how my research work evolved during my PhD study intertwined with my clinical training and foreign fellowships, **the main aims of this dissertation are organized into three major groups**, and subsequently corroborated into specific aims.

- First aim is associated with studies using unique experimental behavioural and non-traditional neuropsychological tests aiming at timely diagnosis of AD;
- Second aim is associated with non-invasive evaluation of participants with preclinical AD and at-risk cognitively unimpaired individuals;
- Third, the largest aim, is associated with studies on multimodality imaging in DLB to better understand the complex biology of DLB.

2.2. Aim 1. To utilize experimental neuropsychology tasks as potential markers of early AD and to determine their clinico-anatomical associations with structural imaging.

2.2.1. Study I: The specific aim of study I was to investigate whether allocentric spatial navigation impairment is proportional to right hippocampal atrophy, regardless of the whole

brain atrophy, using the human analogue of Morris water maze.

Second objective was to compare the spatial navigation scores of humans navigating the task in real space to scores from the simplified computerized test given the practicality and transferability of computer testing.

We had these three specific hypotheses: 1. Allocentric spatial navigation accuracy would be proportional to the right hippocampal volume (atrophy) irrespective of the whole brain atrophy. This would indicate the allocentric spatial navigation is the associate of the right hippocampal volume specifically, and not the whole brain volume.

2. The relationship between allocentric spatial navigation performance and the right hippocampal volume (atrophy) would be stronger in those elderly with a cognitive impairment compared to those cognitively intact

3. Results from the real-space 3-dimensional setting would correlate with the computerized 2-dimensional test, with practical implications of this finding.

2.2.2. Study II: The specific aim of study II was to investigate whether so called self-centered (egocentric) and world-centered (allocentric) spatial navigation performance could be differentiated from the established, paper-and-pencil cognitive functions such as verbal and nonverbal memory, executive and visuospatial functions, attention and working memory, and language function.

Specifically, we hypothesized that: 1. Performance from paper-and-pencil based neuropsychological tests in the six established domains (attention and working memory, executive and visuospatial, nonverbal and verbal memory and language) would be separated from performance in allo- and egocentric spatial navigation task in a factor analysis, suggesting that separate underlying mechanisms of spatial navigation vs other cognitive domains;

2. However, the performance in the six established cognitive domains would still be associated with allocentric and egocentric spatial navigation;

3. Right hippocampal volume, which is both, a structure impaired early on in AD course, and a structure important for allocentric navigation, would be preferentially associated with performance in allocentric navigation task than with performance in memory test.

2.2.3. Study III: The specific aim of study III was to examine emotional prosody recognition (EPR) in participants with aMCI due to AD, AD dementia patients, and

cognitively unimpaired controls, and to determine the associations of EPR performance with measures of the regional brain volumes or cortical thickness.
In addition, the EPR score was associated with a cognitive impairment by MMSE. Using the receiver operating characteristic (ROC) analysis, the effectiveness of EPR tests to distinguish the control group from the aMCI and dementia groups was tested.
We specifically hypothesized that: 1. EPR is increasingly impaired more in prodromal AD and AD dementia compared to controls;
2. EPR is associated with thickness or volume (atrophy) of specific brain structures implicated in the emotional processing such as temporal pole, STS, anterior cingulate or amygdala.

2.3. Aim 2. To characterize cognitively normal older adults who may be at risk of developing clinically apparent AD using widely available brain imaging method with potential to predict positivity of well-established AD biomarkers such as amyloid PET.

2.3.1. Study IV: The specific aim of study IV was to utilize a single time-point 1H-MRS for predicting longitudinal accumulation of Aß in PET in a sample of clinically unimpaired older adults who may be at risk of future cognitive decline and clinically apparent AD.
We hypothesized that: 1. Levels of certain H-MRS metabolites such as lower myoinositol (a marker of glial activation) or lower N-acetyl-aspartate (marker of neuronal resilience or viability) measured cross-sectionally at baseline would have the capacity to predict the future ß-amyloid accumulation over time in normal older adults;
2. Presence of at risk APOE ε4 status may modify this association;
3. APOE ε4 carriers would accumulate ß-amyloid longitudinally faster than noncarrier several studies imply this, but so far, none of them proven this longitudinally.

2.4. Aim 3. Because AD frequently overlaps with DLB which can obscure the DLB diagnosis and cause the patients with mixed pathologies to deteriorate faster and survive shorter, this aim focused on disentangling DLB-related and AD-related imaging findings and to determine the associations of imaging findings with clinical phenotype and clinical progression in DLB.

2.4.1. Study V: The specific aim of study V was to investigate the pattern and the

magnitude of longitudinal rates of atrophy in autopsy-confirmed DLB patients and to investigate the correlations of the rates of atrophy with clinical progression in autopsy-confirmed DLB patients.

We hypothesized that 1. DLB autopsy-confirmed patients would have low rates of atrophy over time but those with mixed DLB/AD pathology would have significant rates of atrophy.
2. Higher rates of atrophy would be associated with faster clinical and cognitive decline.
3. We modelled the sample size estimations for a hypothetical clinical trial recruiting patients with DLB and mixed DLB/AD pathologies where rates would be used as surrogate outcome measures.

2.4.2. Study VI: The specific aim of study VI was to determine white matter impairment in DLB patients using DTI technique and to determine the effect of Aß load by PET on the white matter integrity in DLB;

We hypothesized that the disruption of white matter in DLB patients would be of different distribution and smaller magnitude than in AD patients, and that AD-related pathology represented by amyloid load from PET may contribute to the white matter disruption in DLB patients.

2.4.3. Study VII: The specific aim of study VII was to assess the patterns of cortical hypoperfusion using a noninvasive arterial spin labelling MRI in DLB patients compared to more invasive and expensive glucose FDG PET, and to assess the effect of AD-related pathology on the pattern of cortical hypoperfusion in DLB patients.

We hypothesized that: 1. The newly determined voxel-wise pattern of perfusion MRI would be similar to traditionally used but invasive glucose metabolism on PET;

2. The CIS ratio would be similar across the both imaging methods in DLB patients, supporting the interchangeability of both imaging methods;
3. Overlapping AD tau-related pathology by tau PET would cause CIS ratio to lessen and visual CIS to disappear on both ASL MRI and FDG-PET. Lower CIS ratio would be associated with clinical and cognitive progression in DLB patients.

2.4.4. Study VIII: The specific aim of study VIII was to determine the trajectory of longitudinal Aß accumulation in DLB patients and associations of longitudinal Aß accumulation with clinical and cognitive decline over time.

We hypothesized that the trajectory of longitudinal Aß accumulation in DLB patients would not be linear, based on the known trajectories of various AD biomarkers assessed in AD continuum patients. However, because similar studies have never been performed in the DLB patients and this was the first study ever to assess AD longitudinal biomarkers in DLB, our approach was more data-driven than hypothesis-driven.

2.4.5. Study IX: The specific aim of study IX was to investigate the pattern and magnitude of both, regional cross-sectional and regional longitudinal rates of atrophy in patients with prodromal DLB (MCI-LB) and associations of atrophy rates with clinical disease progression.

We hypothesized that the regional cross-sectional atrophy would localize to basal forebrain (nucleus basalis of Meynert) in MCI-LB as previous studies demonstrated a profound cholinergic deficit in DLB patients and that DLB patients respond well to AChEI treatment. However, we hypothesized that the longitudinal rates of atrophy would reveal more wide-spread patterns of atrophy compared to snapshot-like cross-sectional measurements in these MCI-LB patients. We also hypothesized that regional rates of atrophy would correlate with longitudinal measures of clinical and cognitive decline in MCI-LB patients.

2.4.6. Study X: The specific aim of study X was to assess different aspects of cerebrovascular disease (CVD) in a multinational cohort of DLB patients and to ascertain the contribution of cerebrovascular disease to clinical phenotype in DLB using a multi-site international cohort.

Previous studies on cerebrovascular disease in DLB have been sparse and equivocal in terms of CVD contribution to clinical phenotype of DLB patients. **We hypothesized** that DLB patients would show relatively significant CVD in their brains, and that the overlapping CVD would obscure the expected clinical phenotype in DLB patients.

3. Methods

3.1. Study participants and underlying cohorts

Studies I, II, III under **Aim 1** and collaborative **study X** under **Aim 3** have been performed within the **Czech CBAS cohort** at the Cognitive center, Department of Neurology, Motol University Hospital and the Second Faculty of Medicine, Charles University in Prague, with a major structural and grant support from several funds including European Union funds, namely Project LQ1605, II MEYS**,** GAUK 624012, AZV NV18-04-00346, Project LX22NPO5107 – Next Generation EU in collaboration with Brno site, the International Clinical Research Center, St. Annes' University Hospital Brno.

Study IV under **Aim 2** and **studies V-X** under **Aim 3** have been performed within the cohorts at **Mayo Clinic Rochester**, United States, with a structural and grant support from the major research-supporting institutions in the United States and some of the studies with my partial personal support from LQ1605 project by MEYS.

3.1.1. The Czech Brain Ageing Study - CBAS

The CBAS is, to our knowledge, the first large, prospective, observational cohort study in Central Europe on ageing and dementia (Sheardova et al., 2019). CBAS was initiated to investigate the potential of early (bio)markers introduced by the study organizers themselves or by adopting the potential novel biomarkers from external collaborators. CBAS has been investigating risk and protective factors associated with the cognitive decline and dementia by recruiting relatively large numbers of older adults, recording detailed infor-mation on medical history, current and recent lifestyle choices, social environment, education, genetic, physiological, laboratory and biofluid measures, and examining clinical and cognitive status and brain imaging longitudinally. CBAS is multicentric, memory clinic-based cohort study which has been enrolling older adults 55+ years old who do not have dementia at the baseline. Memory clinics are associated with two major university hospitals in Prague: Motol University Hospital and in Brno: St. Anne's University Hospital. Whereas Prague site constitutes predominantly an urban cohort, Brno site also constitutes a rural cohort. Most of CBAS participants are volunteers, who initially visit as self-referrals,
or are referred by family members, general practitioners, various specialists or sometimes
by other sites such as Czech Alzheimer Society units across the country. Participants are offered the standard clinical evaluation aligned with standard clinical practice and covered by their health insurance. If they meet inclusion criteria, agree on the research participation,

and sign an informed consent, they can be enrolled into CBAS at which point they undergo a larger panel of examinations including experimental ones such as spatial navigation. CBAS also enrols and follows-up participants who already have dementia including AD dementia and other neurodegenerative dementias and lesions such as DLB, FTLD, atypical presentations and vascular lesions. This smaller cohort is labelled as CBAS+.Cognitively unimpaired older adults who are designated as 'controls' for comparison purposes are often recruited from the volunteers attending the University of the third age, the Second Faculty of Medicine, Charles University or from the partners or age-corresponding family members of CBAS patients.

Participants recruited into CBAS are invited for a clinical visit comprising the neurologic examination, MRI at 1.5T or 3T, and are evaluated using a complex neuropsychological battery. CBAS participants have various biomarker modalities evaluated. Those who are judged as having other major neurological, psychiatric, or systemic condition potentially interfering with cognitive performance are excluded. Most CBAS participants fall within SCD or MCI stages of (AD) continuum.

CBAS participants are followed up longitudinally using a predefined procedure. Cognitively unimpaired controls and those with SCD are followed-up biannually. MCI patients and those with dementia are followed-up annually, or the follow up is scheduled when there is a suspicion they might have progressed from MCI to dementia (converters). The CBAS neuropsychological battery (Nikolai et al., 2018) is similar to the Uniform Data Set battery (Weintraub et al., 2009) which has been used in other major studies such as Harvard Ageing Brain Study at Massachusetts General Hospital, Boston, or Mayo Clinic Study of Ageing at Mayo Clinic Rochester. CBAS psychometry also includes various challenging experimental memory tests to address an early memory impairment. Multiple lifestyle (sleep, spirituality, physical activity, falls, positive psychology) questionnaires are administered to the participant or their proxy, detailed medical history is taken, basic physical measures such as height, weight, blood pressure, and basic blood tests are sampled. Genotyping of selected genetical factors is performed, such as APOE ε4. In a subset of participants, spinal tap to obtain CSF and/or amyloid PET are performed to determine the biomarker status. Recently, biofluid based biomarkers have been introduced as well. The bio samples are archived in a designated biobank using the established standard processing and storage methods (Vanderstichele et al., 2012).

CBAS collaborates with other Czech sites and has a number of active international collaborations. Public website of the CBAS can be accessed at www.cbas.cz

The CBAS study has been described in detail in a publication by Sheardova, K., Vyhnalek, M., Nedelska, Z. et al., in 2019 in *BMJ Open* listed as a supportive publication of this thesis (Sheardova et al., 2019).

3.1.2. The Mayo Clinic Study of Ageing and the Mayo Clinic Alzheimer's Disease Research Center

Both, the Mayo Clinic Study of Ageing (MCSA) and the Mayo Clinic Alzheimer's Disease Research Center Rochester (ADRC) are longitudinal observational cohort studies with serial evaluations (Roberts et al., 2012).MCSA is a population-based cohort focused on ageing, located in the Olmsted County in Minnesota, USA. The cohort enrols older volunteers without dementia. Serial visits are planned every 15 to 18 months, and include neuropsychological evaluations using comprehensive tests spanning all cognitive domains, clinical stageing, brain imaging with multimodality MRI and multimodality PET (glucose, amyloid and tau PET) and a variety of more experimental brain and body imaging methods. Approximately n = 2800 participants have been actively followed-up in the present, and approximately n = 11000 have been longitudinally examined all-time. The final diagnosis of an individual is achieved during a panel consensus by the examining physician, nurse, and neuropsychologist. The panel also evaluates participants' profession, and sensory impairment (hearing and eyesight) in ADRC participants are enrolled from the community and regional patients referred to ADRC. Each patient undergoes a standardized evaluation administered by a relay of professionals from study nurse to behavioural neurologist to psychometrist, using well-established scales and scores Geriatric Depression Scale, Activities of Daily Living, family and medical history, neurological examination, and Hachinski Ischemic Scale. Blood comprehen-sive laboratory and APOE genotyping are performed, followed by a multimodality imaging. Panel consensus is performed periodically to determine the concurrent diagnosis with respect to currently valid (or favoured) diagnostic criteria and blinded to previous panel consensus diagnosis attained earlier. Included is information on education, previous professsion, and eye and hearing impairment record.

3.1.3. European Dementia with Lewy Bodies consortium

Both, Czech CBAS cohort and Mayo Clinic ADRC collaborate with European Dementia with Lewy bodies consortium (E-DLB) which is a multi-center and global scientific initiative with a main objective to establish international consensus diagnostic criteria for

DLB and more recently a diagnostic guideline for prodromal DLB stages, and to create representative and high-quality biomarker data. The study originated as a retrospective, but now continues as prospective longitudinal observational cohort. Further mission of this consortium is to organize the translational clinical research and clinical trials aiming at DLB and improving the quality of life and other outcomes of patients with DLB.

Study under **Aim 3**, **specific aim X** was conducted using this E-DLB platform. Several other publications have been prepared jointly with this platform and they are listed in supportive bibliography of this thesis.

Website of the E-DLB can be accessed at www.e-dlb.com

3.2. Data management

The personnel of the CBAS, both Mayo Clinic studies and E-DLB is multidisciplinary. Within each study, the expert cores operate to guarantee the accuracy and the quality of the data collected, such as imaging core (MRI), neuropsychology, molecular imaging (PET), genetics and biofluid-based core. The administrative supportive personnel guarantee the patient scheduling and basic data organization and deposition into an encrypted database designed to store and manipulate pseudonymized patient and volunteer data and findings.

In the CBAS and both Mayo Clinic studies, Redcap setting is utilized to store the data in the database. This setting was chosen because it is an appropriate carrier of this type of epidemiological data designed as longitudinal observational studies with repeated follow ups and multiple dependent modalities (coupled evaluations within a given cycle or visit).

When a particular experiment is decided, various data modalities are pulled out ad hoc – on a request. Often, they are ready to be processed in a specific statistical analysis. Other times, such as with neuroimaging data, these need to be processed using appropriate algorithms. To ensure the necessary data protection, good research ethics and current legislature, all data are stored as pseudonymized, thus, external personnel or the public, nor the participants themselves cannot retrospectively identify the donor of a particular set of variables.

3.3. Experimental neuropsychology in CBAS Prague relevant to this dissertation

3.3.1. The spatial navigation testing by the Hidden Goal Task

The Hidden Goal Task (HGT) used in the Study I and Study II under Aim 1 is performed in a 2dimensional virtual environment on the computer screen (Laczo et al., 2012a; Laczo et

al., 2014) and in a 3-dimensional real environment of the blue velvet arena (BVA), and is designed primarily to examine *egocentric* and *allocentric* strategies of spatial navigation. Furthermore, the Hidden Goal Task paradigm allows for examining the allocentric delayed spatial navigation. During this task, the participant is requested to find the accurate position of a hidden target (goal), which is projected as a circle-shaped light onto the arena floor by a projector in the real time. The location of the hidden target can be accurately localized using the specific navigational cues. These cues can be the starting position of a participant, hence the egocentric spatial navigation. Alternatively, the target can be localized using the position of the orientation cues projected at the perimeter of the BVA, hence using the allocentric strategy of spatial navigation. The task is first performed in a virtual environment on the computer screen, and subsequently in a real environment of the BVA. Instructions are given and the practice trials are performed at the beginning. The examination phase of the task consists of 4 subtasks in a predefined order and of an increasing difficulty: mixed ego and allocentric providing the most navigational cues to aid the target location, followed by the egocentric, allocentric and then allocentric delayed. First 3 tasks have 8 trials each to locate the target. After each trial, the participant is shown the correct target position to provide them with feedback and to show the potential difference between correct target's position and position chosen by the participant. This allows for the learning effect which can be tracked as an improvement over the course of trials. In the 4th task, the allocentric delayed, administered 30 minutes later, there are 2 trials only and the original position of the target is not revealed to the participants. As the tasks proceed, the absolute positions of the start, navigational cues at the perimeter and the position of the target do change into a new position in a sense that the whole configuration is rotated several degrees to the left or right, but spatial relationship and angles among the points of interest remain unchanged. In more detail, in task 1, the participants can orient themselves using their own starting position and the orientation cues projected to the perimeter and can therefore use both egocentric and allocentric strategies. In subtask 2, the participants can only orient themselves using their start position, as there are no navigational cues available at the perimeter, and thus the focus is on examining the egocentric strategy. In subtask 3, only navigational cues at the perimeter can be used for orientation, but the position of the start is deliberately changed to a different one, letting the participants know this; hence they no longer can use the start position. This phase is thus focused on examining the allocentric strategy. In subtask 4 administered with a deliberate 30 minutes delay after all previous tasks, only navigational cues can be used for orientation, similar to subtask 3. The main metrics or the outcome of the spatial navigation

testing is the distance error in pixels in computerized version or in centimetres in the real space version. The distance error informs about the accuracy of the spatial navigation performance in a sense that it demonstrates the distance between the presumed target's position chosen by the participant, and the true position of the target that is predefined.

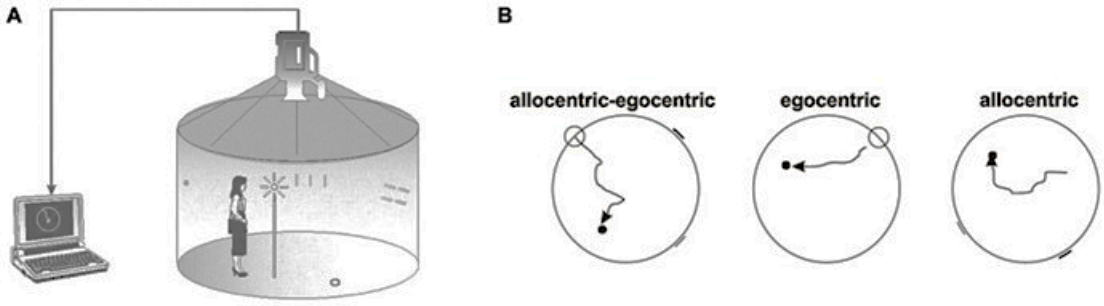


Figure 14. shows A. the real-space 3-dimensional setting of the Hidden Goal Task called the Blue Velvet Arena and B. the schematic of the 2-dimensional computerized version with specific subtasks associated to specific strategies of spatial navigation. Adapted image, courtesy of Dr. Kamil Vlcek (Gazova et al., 2013)

3.3.2. The prosody test of emotion recognition from vocal recording

The experimental battery for the Emotional Prosody Recognition Test (EPR) in **Study III** under **Aim 1** was developed in partnership with four professional actors who made 200 recordings using two neutral semantic meaning sentences in Czech language: "The table has four legs" or "Dogs that bark do not bite". Two male and two female native speaker actors were requested to generate a distinct emotional tone of voice of 3 seconds in duration for each of the following emotions: rage, disgust, sorrow, fear, and joy. Hence, each emotion was equally represented using 40 recordings. From this extensive recorded dataset, 88 cognitively normal volunteers recruited from the clinical personnel of Motol University Hospital, of mean age 32 years with equal distribution of females to males, selected the most representative emotional voice recordings to construct the experimental battery. Volunteers were relatively young because the test was initially designed for assessment of epilepsy patients, who are on average younger than typical AD patients. The last experimental test featured 25 recordings of 3 second duration each, spoken by one female and one male native speaker professional actor. Despite the neutral semantic meaning of the sentences, these recordings had emotionally charged voices portraying sorrow, joy, fear, disgust, and rage; hence, each emotion was portrayed five times. Study participants were exposed to the emotional voice recordings on a computer utilizing the headphones. The set of emotional voice recordings were played to each participant in the same sequence under the constant

supervision of the qualified test administrator. After each recording, participants were required to identify/choose the most accurate emotion from the presented written list of these five emotions. There was no time constraint to prevent or decrease the test-related anxiety or stress. The test administrator repeated the instruction to choose one most appropriate emotion from the presented written list and waited until participant selected each time. After each recording, the attempt was graded as accurate or inaccurate, thus the maximum score of 25 points. Methods are detailed in a paper that is included in this thesis (Amlerova et al., 2022).

3.4. Brain imaging

3.4.1. Imaging in The Czech Brain Ageing Study relevant to this dissertation

Participants from **Studies I-III, Aim 1** and collaborative **Study X, Aim 3** are scanned at baseline visit and at follow-ups at 1.5T Siemens Avanto scanner if not contradicted to obtain brain MRI for clinical purpose and for clinical research. The scans include clinical sequences such as T1-weighted or T2-weighted images to ascertain possible focal findings such as meningioma or normal pressure hydrocephalus, or older cortical and subcortical infarcts, important for the differential diagnosis and excluding patients who may have significant comorbidities to their cognitive impairment. T2* sequence is used to count the microbleeds that could be associated with cerebral amyloid angiopathy. Diffusion weighted sequences are used to ascertain a recent ischemia. Fluid Attenuated Inversion Recovery (FLAIR) images are included to rate the white matter hyperintensities as imaging correlate of small vessel disease, which is frequent in Czech patients. Memory clinic physicians apply various appropriate visual rating scales to semiquantitatively rate the most common imaging findings and degree of whole brain and regional atrophy for clinical purpose or to exclude the individuals with overt cerebrovascular pathologies from clinical research. The protocol was designed as 'ADNI'-like, to be potentially harmonized with other larger imaging studies in ageing and dementia. ADNI (Alzheimer's Disease Neuroimaging Initiative) (Weiner et al., 2012) is one of the largest, multi-site longitudinal brain imaging studies in the world since mid-2000s'.

The imaging protocol includes the T1-weighted high resolution 3-dimensional volumetric magnetic-prepared rapid echo inversion recovery (MPRAGE) sequence which is suitable for volumetry of brain structures and cortical thickness. In most instances, we utilize a freely-available automated algorithm FreeSurfer to measure regional volumes and cortical thickness. FreeSurfer has been a robust, widely used tool will an excellent documentation

and continuos development since early 2000s' by the Laboratory for Computational neuroimaging, Athnoula A. Martinos Center for Biomedical Imaging affiliated with MIT Boston. The algorithm has been designed to quantitatively analyse and visualize brain MRI data in cross-sectional and longitudinal studies. The pipeline is well documented at official: https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki.

The implementation into CBAS studies is detailed in manuscripts under Aim 1 (Amlerova et al., 2022; Laczo et al., 2017).

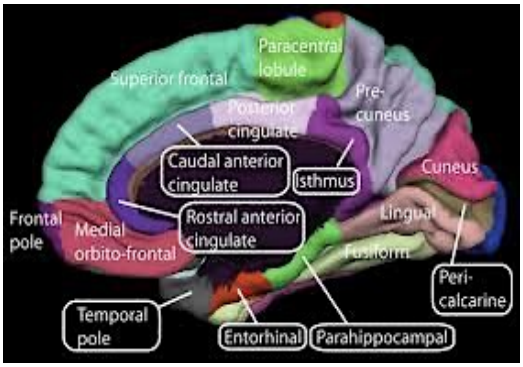


Figure 15. shows colour-coded regions of the cortical parcellation performed by the FreeSurfer algorithm using an embedded Desikan-Killiany atlas for cortical (Desikan et al., 2006). The image is sourced from the freely available documentation FreeSurferWiki.

The technical acquisition parameters are detailed in manuscripts published under Aim 1.

The MRI from the study I in Aim 1 were scanned at 1.5T Philips scanner. Technical details of the acquisition sequence are described in Nedelska et al., 2012 (Nedelska et al., 2012).

3.4.2. Imaging in the Mayo Clinic Study of Ageing and Alzheimer's Disease Research Center studies

Alzheimer's Disease Imaging Research (ADIR) laboratory at Mayo Clinic, affiliated to the Department of Neurology and Radiology and both Mayo Clinic studies on ageing and dementia is one of the largest operating groups. They also coordinate imaging activities under ADNI multisite imaging initiative. The laboratory operates under the leadership of Dr. Clifford Jack who proposed the hypothetical model of AD biomarkers, and previously the co-leadership of Dr. Ronald Petersen who first suggested the syndrome of mild cognitive impairment. The difference from most of clinical research laboratories affiliated with memory clinics, such as Czech CBAS, is that the American group employs several biomedical imaging experts full time, such as image algorithm developers, programmers, biomedical engineers, mathematicians, physicists, image analysts, neurologists, statisticians

and radiologists in order to produce the most optimal imaging tools and data analysis approaches in the house. Therefore, the imaging sequences in MRI modalities and in PET modalities are optimized here or developed in collaboration with main manufacturers such as Siemens, General Electric (GE) and others. Volumetric, diffusion imaging data and other quantitative algorithms for data analysis and visualization are developed or optimized here.

The Mayo Clinic Adult Lifespan Template (MCALT) is a prerequisite for all imaging MRI and PET projects at this center. It has been developed by Dr. Christopher Schwarz, and together with its accompanying atlases such as AAL atlas (depicted below) were made accessible to the public to offer a template suited for the requirements of ageing and AD population research. It is recognized that population-matched templates enable more precise quantitative MRI analysis, however most MRI standard templates are derived from younger individuals. Unlike these, the MCALT is designed to analyse MRI scans of adults aged 30 and older. MCALT was created for use with Statistical Parametric Mapping version 12 but may be used with other segmentation applications. The pipeline is made publicly available by Dr. Schwarz at https://www.nitrc.org/projects/mcalt/.

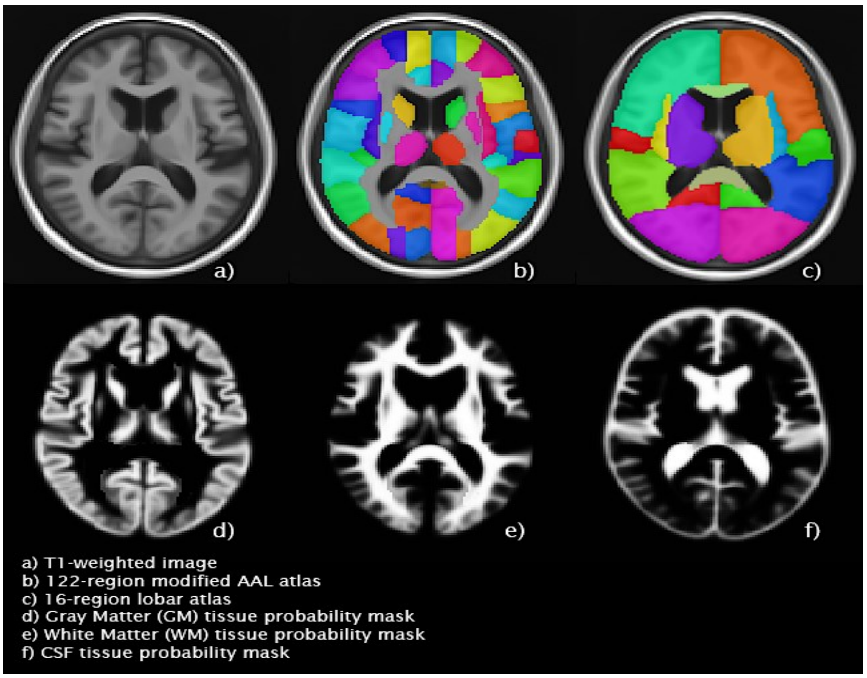


Figure 16. shows MCALT template and including its main components and atlases. Image is courtesy of Dr. Christopher Schwarz publicized at https://www.nitrc.org/projects/mcalt.

The specific acquisition sequences and image data analysis of all MRI images and PET methods used in **Studies IV - X** under **Aim 2** and **Aim 3** are detailed in the published manuscripts under these aims.

3.5. Approach to data analysis and statistics

The study designs typically used in the experiments presented in this dissertation are case-control studies, cross-sectional or longitudinal in their nature, or prospective observational longitudinal cohort studies. The approach to the data analysis has been discussed with statisticians and performed by statisticians, and the specific statistical tests and models are selected to align with the study design, sample size, distribution of the tested variables and the hypothesis which was tested in each study. Where possible, parametric statistical approach has been applied. If the data distribution was non-normal, the adequate transformations were performed to normalize the data distribution, or nonparametric approach was pursued. Often, because of the differences in age as a main risk factor for dementia, distribution of sex or differences in years of education, these variables were treated as covariates. In other cases, cases and controls were matched on age, sex and potentially other relevant variables. The statistical methods used in each study are published in detail Method section of each study I-X.

4. Results: Overview of studies and commented findings

In this chapter, the overview of the individual studies is provided. Studies are grouped into main three aims corroborated along with their hypotheses in Chapter 2. Here, main results of individual studies and their potential applications are provided. Because all studies have been published, the manuscripts in extenso representing studies I-X are inserted into Chapter 11. Appendix. for practical purpose because the thesis is checked by antiplagiarism software.

4.1. Aim 1: To utilize experimental neuropsychology and cognitive tasks as potential markers of early AD stages and to determine their clinic-anatomical associations with imaging

4.1.1. Study I: Spatial navigation impairment is proportional to right hippocampal volume

Published in **Nedelska, Z**., Andel, R., Laczo, J. et al., 2012 in Proceedings of National Academy of Sciences (Nedelska et al., 2012)

- We showed that the right hippocampus is essential for human allocentric (world-centred) spatial navigation in the real space in patients from AD continuum.

Background: Cognitive decline in patients with AD pathology early during the disease is associated with hippocampal impairment. As disease progresses, cognitive decline deepens and is more associated with relatively extensive, or whole brain atrophy. Deterioration in spatial navigation, characterized especially by poor allocentric (world-centred) navigation that is hippocampus-dependent based on animal and some human studies, may develop in AD patients well before the onset of dementia. Furthermore, previous studies in animal and human physiology suggested that at least some brain functions are lateralized, and spatial navigation may be preferentially associated with the right-sided structures. The aim of this study was to investigate whether allocentric spatial navigation impairment is proportional to right hippocampal atrophy, regardless of the whole brain atrophy, using the human paradigm of Morris water maze.

Second objective was to compare the spatial navigation scores of humans navigating the task in real space to scores from the simplified computerized test given the practicality and transferability of computer testing.

Methods: 42 cognitively impaired individuals with amnestic mild cognitive impairment (n = 23) or mild and moderate AD (n = 19) were compared with n = 14 cognitively intact older controls. All participants had a 1.5 T brain MRI, followed by measurement of the total brain and hippocampus (right and left) volumes using an automated algorithm FreeSurfer. Allocentric spatial navigation performance was assessed using both, the real-space 3dimensional version of the human Morris water maze called the Hidden Goal Task and the matching 2-dimensional computer version test. In these tests, participants were asked to find a hidden target using two navigational cues, irrespective of participants own position, hence using the allocentric spatial navigation.

Results: Controlling for age and sex, total brain and left hippocampus volumes, a smaller right hippocampal volume was associated with poorer spatial navigation ability in both real-space (ß = -0.62, P<0.001) and virtual (ß = -0.43, P = 0.026) navigation test versions. In subsequent analyses, these associations were significant for cognitively impaired participants (P < 0.05) but not for cognitively unimpaired subjects (P > 0.59). The correlation between the real-space and virtual space of the navigation test was significant.

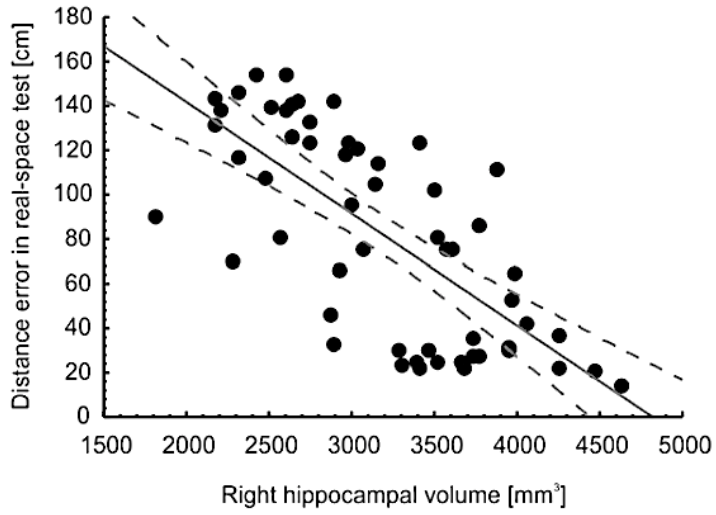


Figure 17. shows an inverse correlation between a smaller right hippocampal volume in mm3 and greater allocentric spatial navigation distance error cm in the real-space version of the Hidden Goal Task, r = -.0.71, p< 0.001 in the patient sample. Subsequent regression modelling adjusting for the most important variables confirmed this association (β = −0.62, P < 0.001).

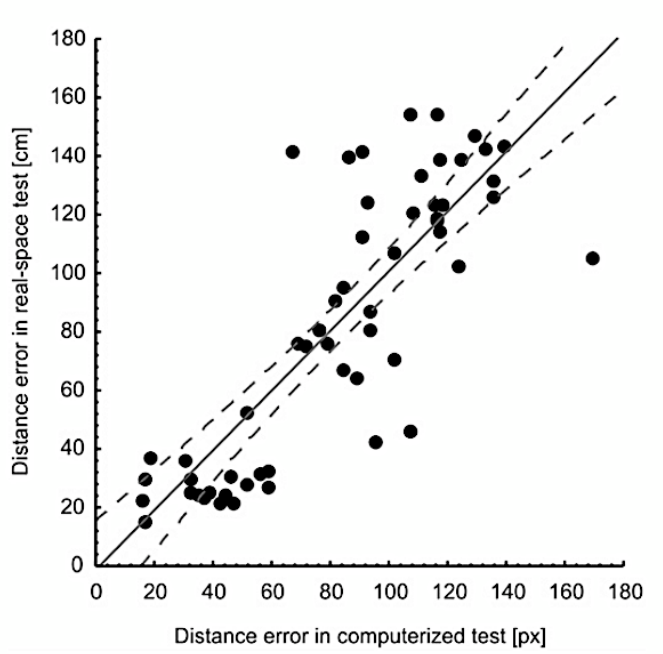


Figure 18. shows a positive correlation between findings from the computerized 2dimensional version of the Hidden Goal Task and the real-space 3-dimensional version, $r = 0.83$, $p < 0.001$. This suggests that although the real-space and computerized version may not be entirely interchangeable, the PC version is a sufficient alternative, especially given its portability and user comfort of administration.

Conclusion: Our findings show that the right hippocampus is essential for allocentric (world-centred) spatial navigation, especially in participants with cognitive impairment. The human version of Morris water maze has the capacity to reflect this association in both, real-space 3dimensional and simplified 2dimensional PC versions.

4.1.2. Study II: Exploring the contribution of spatial navigation to cognitive functioning in older adults

Published in Laczo, J., Andel, R., **Nedelska, Z**. et al., 2017 in Neurobiology of Ageing (Laczo et al., 2017)

- We showed that the spatial navigation domain may be separated from the traditionally established cognitive domains, and that spatial navigation testing of participants with or at risk of AD may provide additional beneficial information to neuropsychology profiling.

Background: Spatial navigation impairment has been documented in AD. This impairment has been associated with hippocampal atrophy. Hippocampus is both, a structure important for spatial navigation and affected by AD-related pathology early on. The aim was to investigate whether so called self-centred (egocentric) and world-centred (allocentric) spatial navigation performance could be differentiated from the established, paper-and-pencil cognitive functions such as verbal and nonverbal memory, executive and visuospatial, language functions, attention and working memory.

Methods: In total, n = 108 older persons (n = 53 cognitively normal controls and n = 55 with aMCI) were evaluated neuropsychologically and tested for spatial navigation performance using a real-space navigational task. A subset of participants (n = 63) had brain MRI with hippocampal volumetry using an automated FreeSurfer. A factor analysis along with a linear regression modelling was used to determine the separability of spatial navigation performance from the traditional cognitive domains.

Results: In a factor analysis, allocentric and egocentric spatial navigation tasks loaded substantially onto the same factor, but other cognitive function-related factors had only modest loadings. In a linear regression, performance in other cognitive domains was not, or was only marginally, associated with spatial navigation performance in control or aMCI groups. Adjusted for age, sex, and education, the right hippocampal volume accounted for 26% of the variation in allocentric spatial navigation performance in the aMCI. However, the hippocampal volume explained proportionally lower variance (up to 14%) in memory compared to variance in allocentric spatial navigation.

Conclusion: Spatial navigation performance, a cognitive associate of an early AD, may be separated from other cognitive functions. To acquire a thorough neuropsychological profile, the additional evaluation of spatial navigation performance may be beneficial.

4.1.3. Study III: Impaired recognition of emotional prosody in Alzheimer's disease

Published in Amlerova, J., Laczo, J., **Nedelska, Z**. et al., 2022 in Alzheimer's Research and Therapy (Amlerova et al., 2022)

- We showed that recognition of emotions from voice is impaired in AD dementia and prodromal AD, which may contribute to the worse interpersonal relationships and quality of life of these patients; and that emotional prosody recognition impairment is associated with the atrophy in rostral anterior cingulate and superior temporal sulcus.

Background: The capacity to comprehend emotions and expressions is frequently impaired in persons with cognitive disorders. Temporal lobe structures, especially right sided, including the anterior cingulate, amygdala, superior temporal sulcus (STS) or temporal pole, have been associated with emotional processing. These regions are affected by AD-related pathology in early stages. The purpose of this study was to examine emotional prosody recognition (EPR) in participants with aMCI due to AD, AD dementia patients, and cognitively unimpaired controls, and to determine the associations of EPR performance with measures of the regional brain volumes or cortical thickness. In addition, the EPR score was associated with a cognitive impairment by MMSE. Using the ROC analysis, the effectiveness of EPR tests to distinguish the control group from the aMCI and dementia groups was tested.

Methods: In total, n = 89 participants from The Czech Brain Ageing Study were examined with the Prosody Emotional Recognition Test (n = 43 aMCI due to AD, n = 36 AD dementia, and n = 23 controls). This test involved the repetition of 25 neutral-meaning statements, each recorded with a distinct emotional prosody (sorrow, fear, joy, disgust, anger). Using the FreeSurfer algorithm software, the amygdala volume and thickness of the temporal pole, STS, and rostral and caudal sections of anterior cingulate were assessed. ANCOVA was performed to assess variations in EPR score. The ROC analysis was performed to evaluate the EPR test's ability to distinguish controls from the aMCI and dementia groups. To investigate associations between EPR scores, structural brain measures, and MMSE, Pearson's correlation coefficients were generated.

Results: EPR was lower in the AD dementia and aMCI groups than in controls. Not only could the EPR total score discriminate between controls and patients, but also between controls and aMCI, controls and dementia, and aMCI and dementia groups. EPR score was reduced in correlation with MMSE as illness severity increased. There was a substantial

positive association between EPR and right temporal pole, STS, and bilateral rostral anterior cingulate thickness.

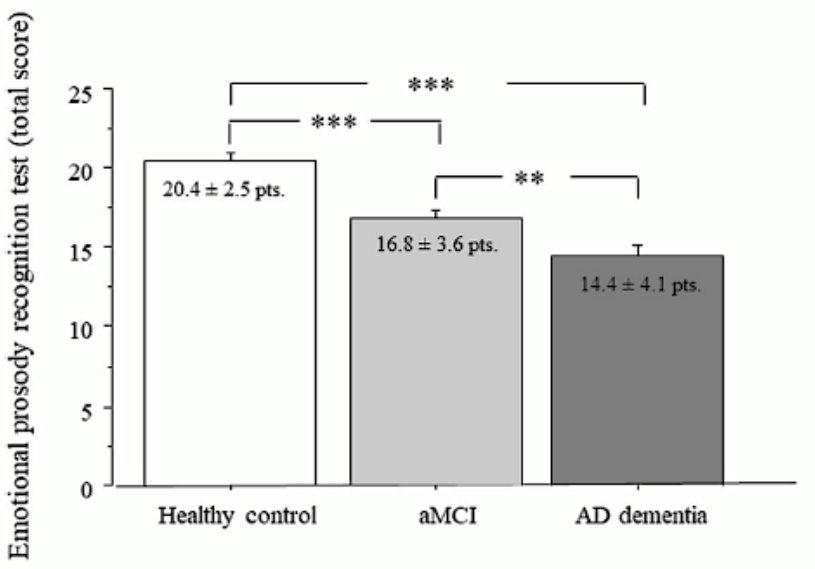


*Figure 19. shows the histograms representing the total emotional prosody recognition scores in prodromal AD (aMCI due to AD) and AD dementia compared to normal control group. **p<0.001, ***p< 0.0001 (Amlerova et al., 2022)*

Conclusion: EPR is diminished in AD dementia and prodromal (aMCI due to AD) patients. These findings suggest that the extensive array of AD symptoms may include emotion deficiencies that exacerbate the patient's quality of life.

4.2. Aim 2: To characterize cognitively normal older adults who may be at risk of developing clinically apparent AD using widely available brain imaging method with potential to predict positivity of well-established AD biomarkers such as amyloid PET.

4.2.1. Study IV: ^{1}H-MRS metabolites and rate of ß-amyloid accumulation on serial PET in clinically normal adults

Published in **Nedelska, Z.**, Przybelski, S., Lesnick, T., et al., 2017 in Neurology (Nedelska et al., 2017)

- We showed that cross-sectional brain metabolite changes from baseline MRS in cognitively unimpaired older individuals can predict subsequent increase in ß-amyloid accumulation on longitudinal amyloid PET. Although carriership of risk APOE ε4 allele does not change this association, we showed that APOE ε4 carriers do accumulate ß-amyloid faster over the time, with implications of more economical identification of apparently normal individuals but at risk of developing AD in the near future.

Background: Many clinically unimpaired older adults have positive ß-amyloid on PET scans. Increased ß-amyloid accumulation can lead to manifest cognitive decline. Proton magnetic resonance spectroscopy (^{1}H-MRS) from a single brain voxel can measure brain metabolites in microscopical concentrations, and the shift in these metabolic concentrations can mirror various pathologic processes on the brain. We aimed at investigating whether a non-invasive and accessible ^{1}H-MRS tissue metabolite measurements taken at baseline can accurately predict an increase in the longitudinal rate of ß-amyloid accumulation as measured by serial PET in clinically normal older adults who are at risk of developing symptomatic AD.

Methods: People aged 60 years and older who were clinically normal at baseline and who had ^{1}H-MRS sampled from the posterior cingulate voxel and longitudinal ^{11}C-Pittsburgh compound B (PiB) ß-amyloid PET with at least two serial scans were included in the study. A total of n = 594 of participants met these criteria and were included in the study. Using mixed-effect models that were controlled for age, sex, and APOE ε4 status, a rate of longitudinal amyloid accumulation was calculated using serial cortical PiB standardized uptake value ratios. The rate of longitudinal amyloid accumulation was estimated as a

function of baseline ^{1}H-MRS metabolite ratios and time. In addition, the effect of APOE ε4 on the association between baseline MRS and an accelerated rate of amyloid accumulation was investigated in the clinically normal older participants.

Results: A greater myo-inositol/creatine ratio (mI/Cr; p = 0.011) and a lower N-acetylaspartate/mI ratio (NAA/mI; p = 0.006) at baseline were associated with an increased amyloid accumulation over time across all individuals, even after controlling for age, sex, and APOE ε4. The link between baseline ^{1}H-MRS metabolite ratios and the rate of amyloid accumulation was not affected by the presence of APOE ε4. However, APOE ε4 carriers accumulated amyloid at a quicker rate than noncarriers (p = 0.001), even though the baseline amyloid load did not differ between carriers and noncarriers.

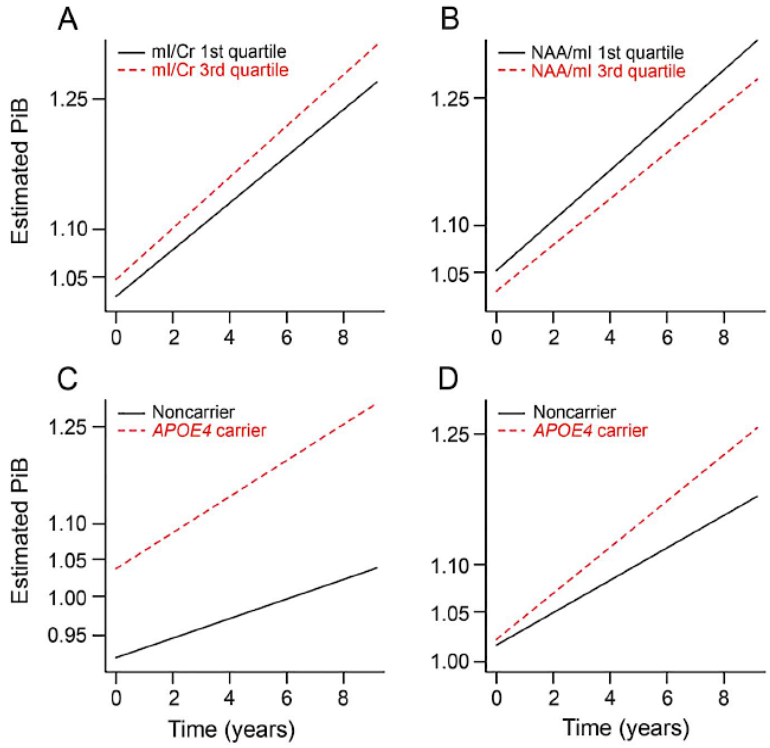


Figure 20. shows the estimates for the rate of ß-amyloid accumulation over time for a clinically normal older participant. Upper line shows the rate of ß-amyloid accumulation is predicted using an interaction between baseline H-MRS metabolite levels and time in a sense that: higher mI/Cr baseline (diverging slopes of the 3rd vs 1st quartile) predicts faster amyloid accumulation over time, and lower baseline NAA/mI predicts faster amyloid accumulation (negative association is shown by inverting the 1st vs the 3rd quartile). Similarly, the lower line shows the differences in longitudinal amyloid accumulation between APOE ε4 carrier who is at risk of cognitive decline compared to ε4 noncarrier who has a lower risk of clinical progression into clinically overt stages. APOE ε4 carriers accumulate amyloid faster than noncarriers, irrespective of their baseline amyloid load (Nedelska et al., 2017).

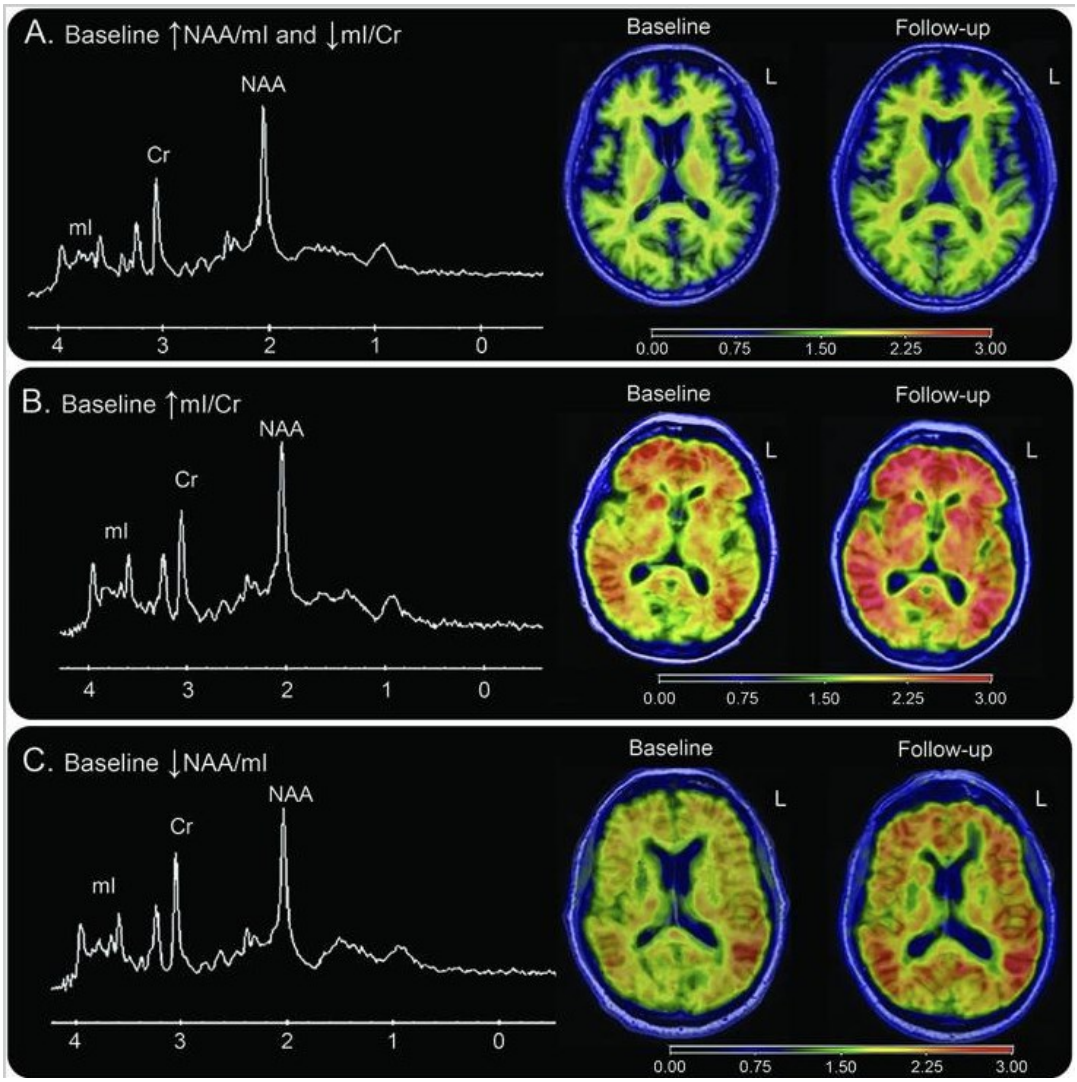


Figure 21. shows three cognitively normal participants, their baseline MRS metabolite levels, their matched baseline amyloid PET and follow-up PET findings. Person A has relatively high NAA/mI and low mI/Cr which can both work as benevolent markers of low amyloid load at baseline and low amyloid accumulation over time. Person B has high baseline mI/Cr linked to quite high (positive) baseline amyloid load and significant accumulation over time. Person C has relatively low baseline NAA/mI and borderline baseline amyloid load but converts to overly amyloid positive on follow-up PET scan (Nedelska et al., 2017).

Conclusion: Early metabolic changes on ^{1}H-MRS and APOE ε4 status are both independently associated with a higher longitudinal ß-amyloid over time in clinically normal older individuals. Because an increased rate of amyloid accumulation in clinically normal older adults may confer a higher risk for the future cognitive decline and mild cognitive impairment, our findings could have important implications for early diagnosis and identification of individuals for secondary prevention trials. MRS is relatively economical and accessible diagnostic imaging method compared to amyloid PET.

4.3. Aim 3: Because AD frequently overlaps with DLB, making the accurate clinical diagnosis more challenging and because patients with mixed pathologies progress faster and survive shorter, this work aimed to use multimodality imaging in DLB to address DLB and AD-related imaging findings and associations with clinical phenotype and disease progression.

4.3.1 Study V: Pattern of brain atrophy rates in autopsy-confirmed dementia with Lewy bodies

Published in **Nedelska, Z.**, Ferman, T., Boeve, B., et al., 2015 in Neurobiology of Ageing (Nedelska, Ferman, et al., 2015)

- We showed that whole brain and temporal regional rates of atrophy over time are minimal, compared to controls, in "pure" DLB patients, but patients with pathologically mixed DLB/AD had rates of atrophy similar to those with "pure" AD. This has implications for diagnostics, prognostication and for designing clinical trials with MRI as surrogate outcome and in patients with mixed pathologies.

Background: On magnetic resonance imaging, patients with DLB have relatively preserved total brain and medial temporal lobe volumes in comparison to patients with AD dementia. The pattern and the distribution of regional brain atrophy rates over time in DLB patients may be influenced, however, by the presence of AD-related pathology, which commonly coexists with DLB. This overlapping pathology may influence the progression and the prognosis of DLB, but data are missing.

Methods: We investigated the pattern of distribution and magnitude of the atrophy rates from two serial MRIs in autopsy-confirmed DLB patients (n = 20) and mixed DLB/AD patients (n = 22), compared with AD dementia (n = 30) and older nondemented control participants (n = 15), who were clinically followed-up antemortem. Serial MRIs taken closest to the death and postmortem examination were used, and both, voxel-wise exploratory approach to see the pattern of differences, and atlas-based approach to see the magnitude of differences were used.

Results: Patients with DLB and with minimal AD-type pathology postmortem had minimal global and regional rates of atrophy on antermortem MRI, similar to those seen in control participants. On the contrary, individuals with mixed DLB and AD pathology showed substantial rates of atrophy throughout the whole brain, as well as in the temporoparietal cortices, hippocampus, and amygdala, along with ventricular enlargement, which were comparable to patients with AD dementia. In patients with DLB and mixed DLB/AD, the atrophy rates longitudinally were correlated with the stage of Braak neurofibrillary tangles on autopsy, the faster progression of cognitive impairment, and the faster progression of motor symptoms.

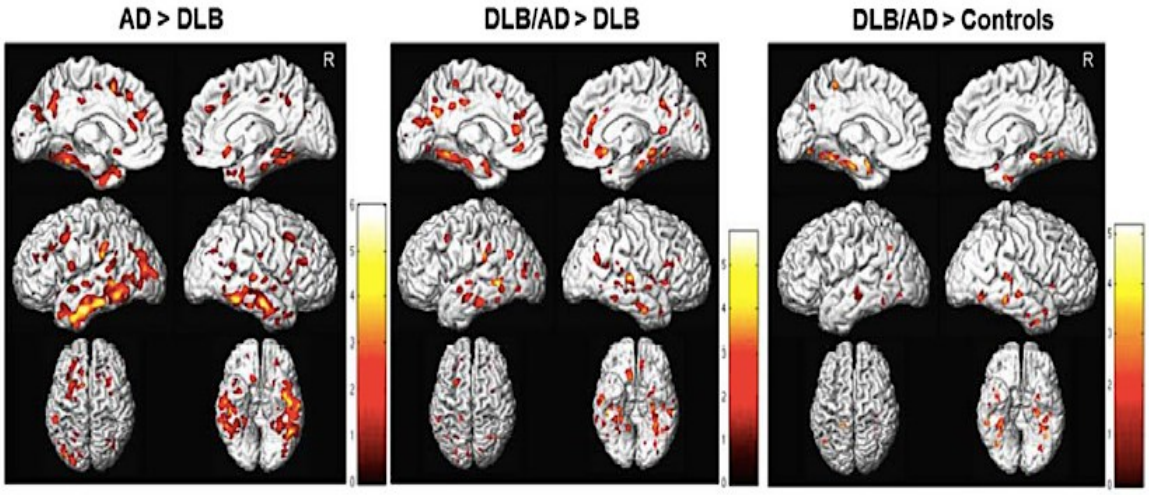


Figure 22. shows the voxel-wise pattern and the regional distribution of cortical rates of atrophy longitudinally between each two autopsy-confirmed groups. DLB vs controls are not shown because there were minimal differences in rates of atrophy (Nedelska, Ferman, et al., 2015).

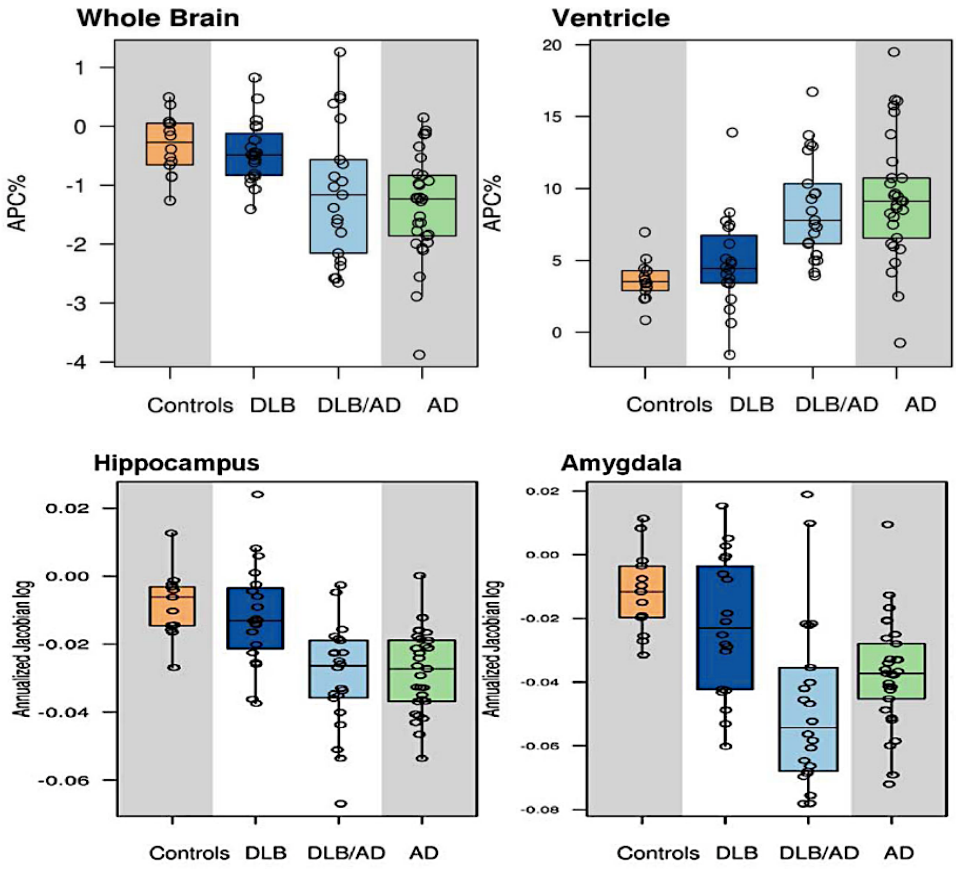


Figure 23. shows the atlas-based differences in global measures of atrophy such as whole brain or expansion of ventricles in the upper row. Lower row shows differences in rates of atrophy in medial temporal regions such as amygdala and hippocampus in the respective autopsy-confirmed groups (Nedelska, Ferman, et al., 2015).

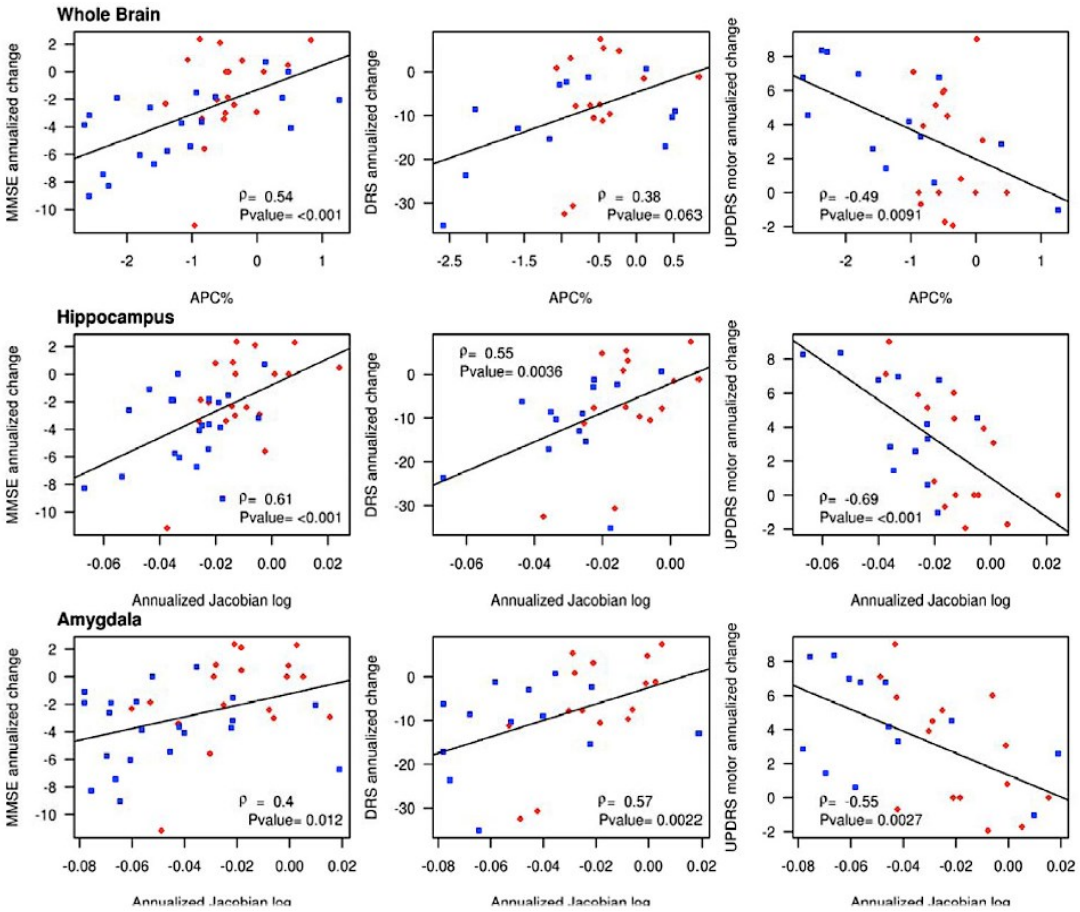


Figure 24. shows Pearson correlations between the measures of cognitive and clinical decline by MMSE, DRS and UPDRS-III motor with the longitudinal atrophy rates (reported as the annualized percentage change, APC or using the transformed Jacobian determinant) in patients with a range of autopsy proven Lewy body pathology (DLB and mixed DLB/AD groups (Nedelska, Ferman, et al., 2015).

Conclusion: The longitudinal rates of atrophy can be employed as indicators of AD-related pathology progression in individuals with primary Lewy body disease. Mixed AD pathology with Lewy body disease leads to faster cognitive decline and disease progression over time, and may have practical implications for patient diagnosis, management, and treatment. Rates of atrophy can be used as surrogate outcomes in clinical trials especially in mixed DLB/AD patients.

4.3.2 Study VI: White matter integrity in dementia with Lewy bodies: a voxel-based analysis of diffusion tensor imaging

Published in **Nedelska, Z.**, Schwarz, C., Boeve, B., et al., 2015 in Neurobiology of Ageing (Nedelska, Schwarz, et al., 2015)

- We showed that that DLB patients have a well-defined impairment of parietooccipital white matter irrespective of intermixed ß-amyloid, but this impairment is associated with hypometabolism of adjacent cortical grey matter. The imaging findings may be helpful in DLB diagnosis and differential diagnosis.

Background: Many individuals who have DLB also have AD-related pathology, which may lead to white matter diffusivity abnormalities on diffusion tensor imaging. Reduced fractional anisotropy (FA) has been associated with white matter damage. The aim of this study was to investigate whether and how presence of ß-amyloid as a marker of AD-related pathology influences the white matter integrity in DLB patients.

Methods: We recruited the consecutive patients with clinically probable DLB (n = 30), AD dementia patients of the same age and sex (n = 30), and cognitively normal controls (n = 60). Diffusion tensor MRI, ^{18}F fluoro-deoxy-d-glucose for cortical functional metabolic impairment, and ^{11}C Pittsburgh compound B PET scans were performed in all individuals.

Results: DLB patients had reduced FA in the parietooccipital white matter indicating white matter impairment in this region, but not in other regions compared to cognitively normal controls. Compared to AD patients, DLB had elevated FA in parahippocampal white matter, indicating relatively preserved parahippocampal white matter in DLB in this region compared to AD. The reduced parietooccipital FA in DLB vs controls remained even after controlling for the effect of AD-related pathology by amyloid load. Similarly, the elevated FA in parahippocampal white matter in DLB vs AD remained even after controlling for amyloid load in DLB. The pattern and the distribution of white matter FA changes shown on DTI was similar to the cortical glucose hypometabolism seen on fluoro-deoxy-d-glucose PET in DLB patients, indicating concomitant impairment of cortices and adjacent white matter in the posterior parietal and occipital regions.

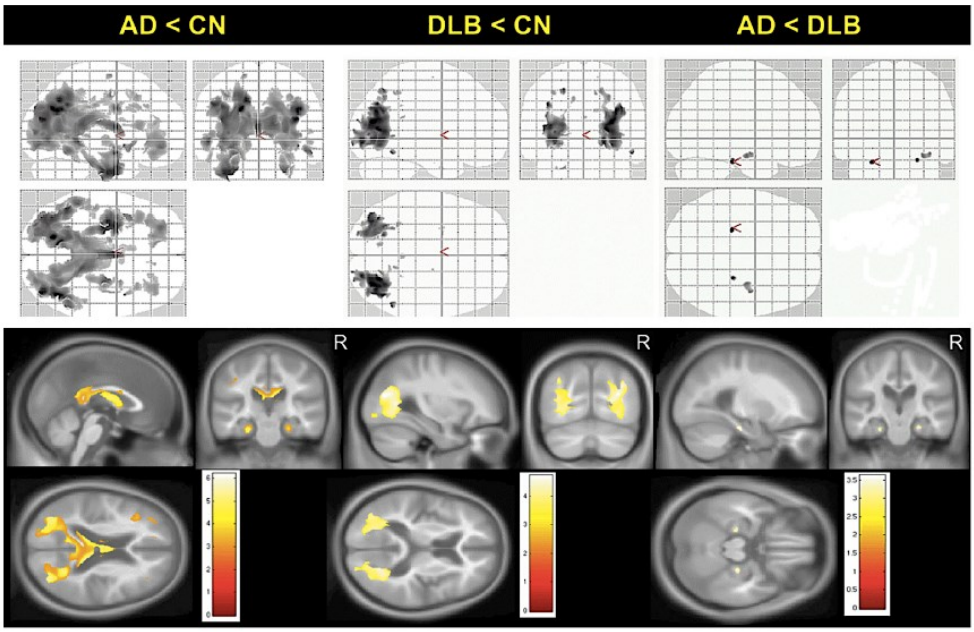


Figure 25. shows the voxel-wise differences between each two clinical groups in white matter integrity by fractional anisotropy derived from DTI. AD dementia patients show the most large-spread patter of white matter disruption, whereas it is more posteriorly distributed in DLB patients. AD patients still have more profound impairment in parahippocampal white matter (Nedelska, Schwarz, et al., 2015).

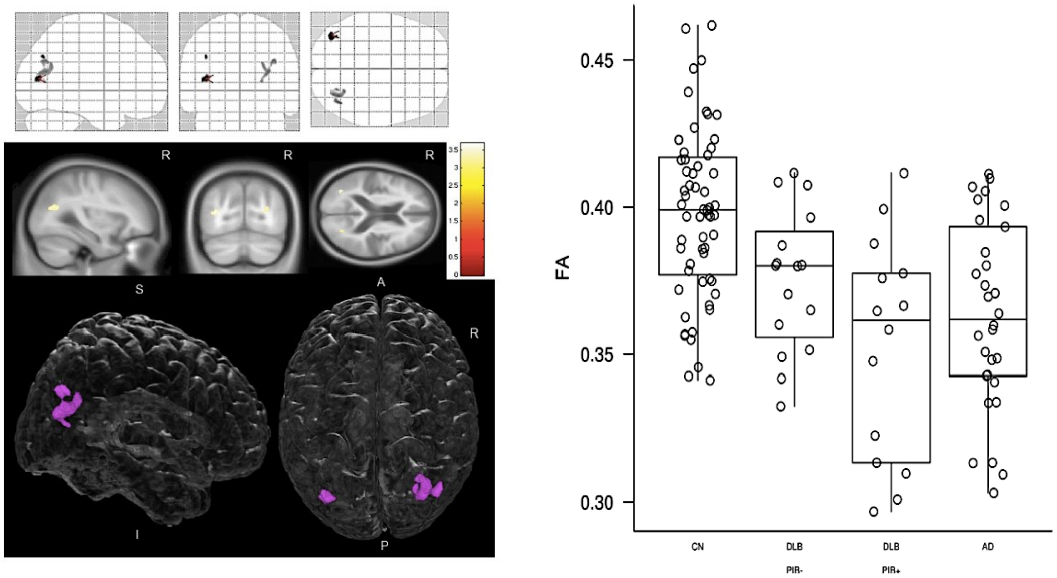


Figure 26. shows voxel-wise well circumscribed impairment of white matter strategically located at the cross-roads posterior temporal, parietal and occipital white matter in DLB compared to controls. This comparison is after adjusting for the effect of amyloid load from PET. Boxplots on the right show lower fractional anisotropy in this white matter parietooccipital region when amyloid load is considered (Nedelska, Schwarz, et al., 2015).

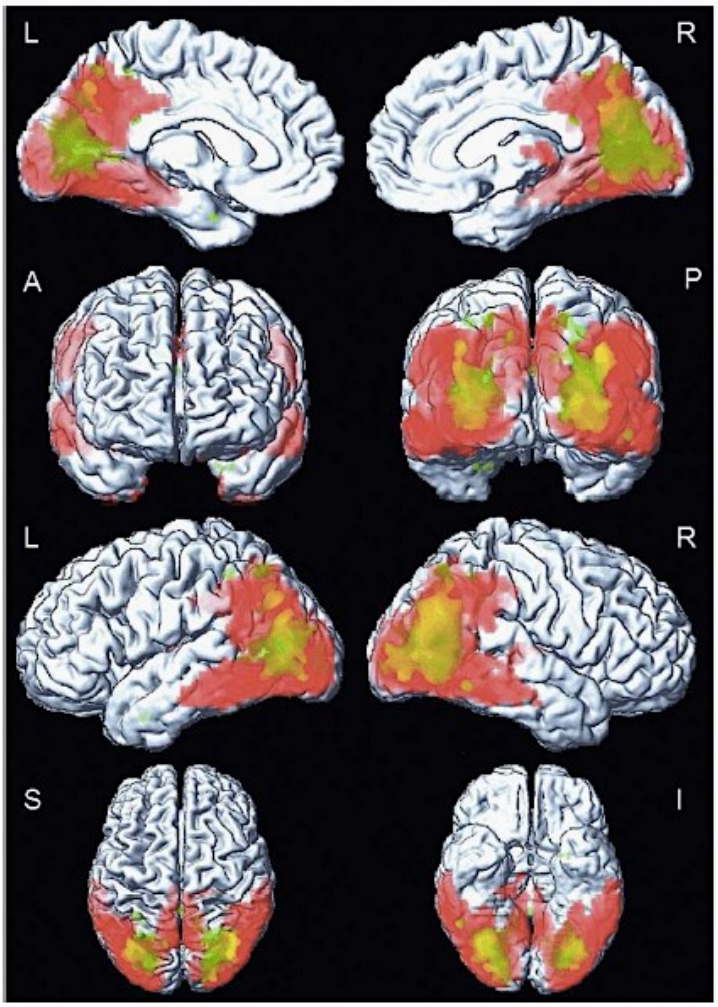


Figure 27. shows the overlay of cortical glucose metabolism impairment (hypometabolism) in red colour and disruption in adjacent white matter in green colour in DLB patients. This finding supports the notion that neurodegeneration of grey matter is associated with the degeneration of white matter or vice versa, although the temporal relationship of these changes cannot be derived from this study (Nedelska, Schwarz, et al., 2015).

Conclusion: DLB is characterized by a loss of parietooccipital white matter integrity, and this loss occurs regardless of the associated amyloid burden as marker of AD-related pathology. Subcortical white matter FA changes are observed in conjunction with adjacent cortical glucose hypometabolism in parietooccipital regions in DLB. The findings suggest a well circumscribed white and grey matter impairment in DLB patients that could aid differential diagnosis of DLB and provide further evidence of interconnectedness of grey matter and white matter processes.

4.3.3. Study VII: Regional cortical perfusion on arterial spin labelling MRI in dementia with Lewy bodies: Associations with clinical severity, glucose metabolism and tau PET

Published in **Nedelska, Z.**, Senjem, M., Przybelski, S., et al., 2018 in NeuroImage Clinical (Nedelska et al., 2018)

- We showed the pattern of cortical hypoperfusion in DLB using relatively more accessible and economical ASL MRI that is like glucose metabolism on traditionally used glucose PET. We showed visually preserved cingulate island sign on ASL MRI as well as a hallmark of DLB. The cingulate island sign wanes with degree of intermixed AD pathology. Findings have diagnostic, differential diagnostic and healthcare planning or economic implications.

Background: On 18 fluoro-deoxy-d-glucose PET, DLB is characterized by visually maintained glucose metabolism in posterior cingulate cortex relative to hypometabolism in precuneus and cuneus. This visual phenomenon is also known as the cingulate island sign (CIS). The CIS, on the other hand, is missing in AD patients. Quantitatively, lower cingulate island sign ratio (i.e., metabolic ration in posterior cingulate cortex/cuneus + precuneus; FDG-CISr) values have been correlated with a more advanced Braak neurofibrillary tangle stage at autopsy in DLB patients. Arterial spin labelling (ASL) is a non-invasive MRI technique used to measure regional perfusion. Assuming that metabolism and perfusion are coupled processes, we aimed at investigating the patterns of regional cortical perfusion and metabolism in DLB patients and the influence of concomitant AD-related pathology in vivo on imaging findings in DLB.

Methods: Using an atlas-based approach, we determined the perfusion cingulate island sign ratio on ASL MRI (ASL-CISr) and its associations with FDG-CISr, tau-PET uptake, and clinical severity in DLB. Our sample (n = 114) consisted of clinically probable DLB patients (n = 19), age-matched patients with probable AD dementia (AD; n = 19), and age-matched controls (n = 76) who underwent MRI with 3-dimensional pseudo-continuous arterial spin labelling, ^{18}F-FDG-PET, and ^{18}F-AV-1451 tau PET. Using voxel-wise statistical parametric mapping, quantitative maps were used to assess the patterns of cerebral perfusion and metabolism.

Results: DLB patients demonstrated hypoperfusion on ASL-MRI in the precuneus, cuneus, and posterior parieto-occipital cortices, but the perfusion in the posterior cingulate gyrus was relatively spared, thus, the CIS similarly to the pattern of hypometabolism on FDG-PET.

ASL-CISr and FDG-CISr were greater in DLB patients than in AD patients ($p < 0.001$), and ASL-CISr was associated with FDG-CISr in DLB patients ($r = 0.67$; $p = 0.002$). ASL-CISr and FDG-CISr had an accuracy of 0.80 and 0.91, respectively, in differentiating DLB from AD patients. In DLB, a lower ASL-CISr was associated with a greater composite medial temporal AV-1451 uptake as surrogate of AD-related pathology ($r = -0.50$; $p = 0.03$). Lower precuneus and cuneus perfusion in DLB was correlated with a more pronounced global clinical impairment by clinical dementia rating scale.

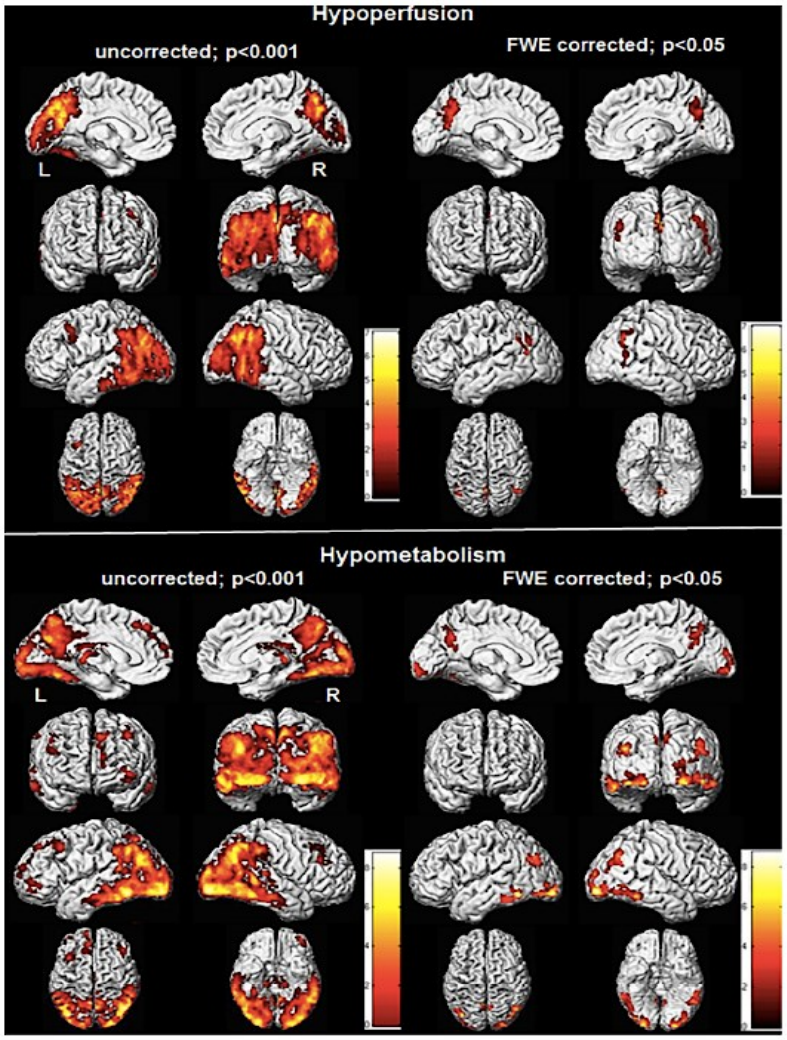


Figure 28. shows voxel-wise pattern – the distribution and the magnitude of hypoperfusion from ASL-MRI compared to pattern of glucose hypometabolism on FDG-PET in DLB patients (Nedelska et al., 2018). The similarities in patterns across these two methods are obvious, supporting the notion that perfusion and metabolism are two processes coupled together, thus the imaging methods potentially interchangeable for practical clinical purposes.

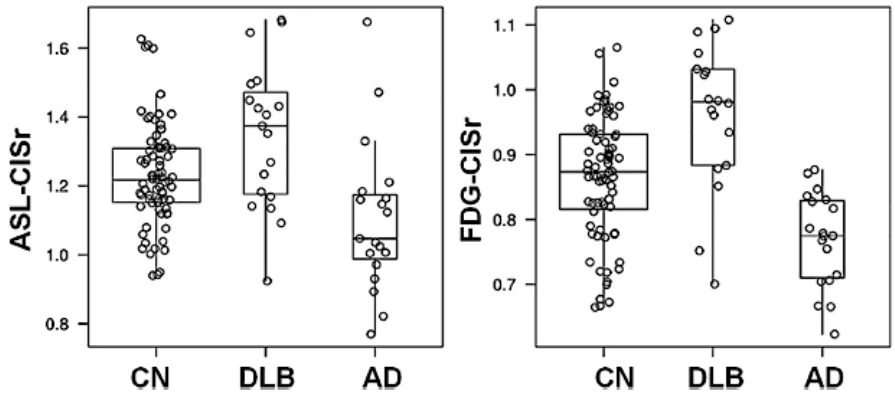


Figure 29. shows the very similar between-group differences in cingulate island sign ratio from ASL MRI (ASL-CISr) and glucose PET (FDG-CISr), the correlation between ratios is r = 0.67, p = 0.002 (Nedelska et al., 2018).

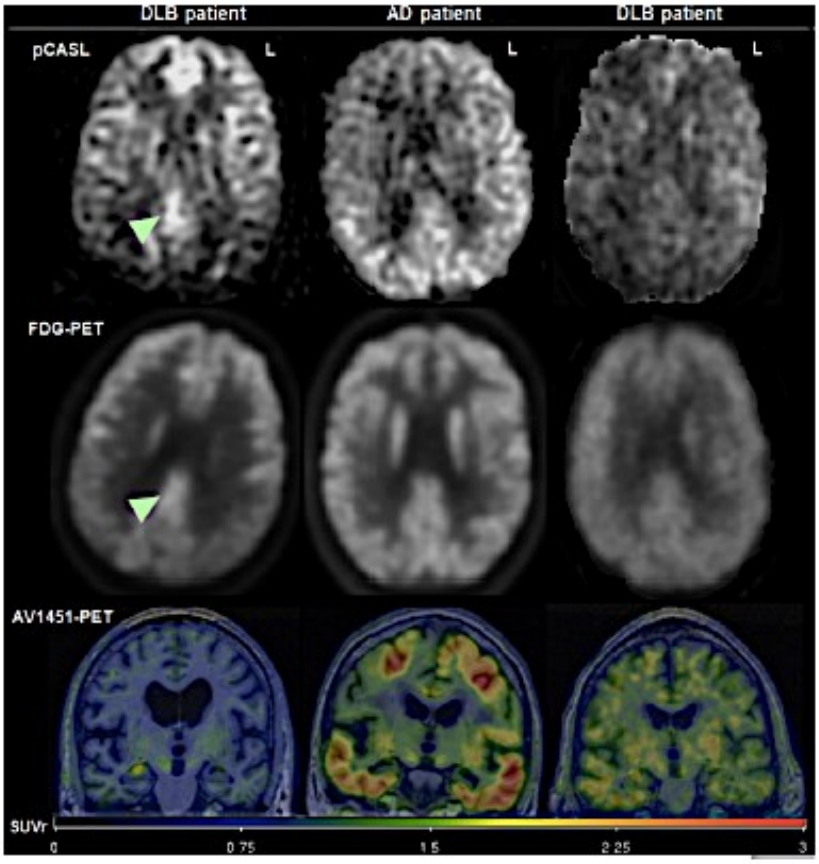


Figure 30. shows three individual patients and their respective findings on imaging methods. Left column is a typical DLB patient with visually preserved CIS (green arrowhead) both on perfusion ASL MRI (labelled as pCASL) and FDG-PET, who has low tau accumulation on AV 1451 tau PET. Middle column is typical AD patient who does not show CIS on any method but has significant tau load on PET. Right column is DLB patient with overlapping AD pathology by some tau load, and because of this, his CIS is lost. Hence CIS is finding specific to DLB and wanes with overlapping AD (Nedelska et al., 2018).

Conclusion: The pattern of cortical hypoperfusion on ASL-MRI is comparable to that of hypometabolism on FDG-PET, and corresponding cingulate island sign ratios correlate with one another in DLB. ASL-MRI may be further developed as a screening and diagnostic assessment tool for DLB patients, especially in clinical situations where FDG-PET is unavailable.

4.3.4. Study VIII: Association of longitudinal ß-amyloid accumulation determined by PET with clinical and cognitive decline in probable dementia with Lewy bodies

Published in **Nedelska, Z.**, Schwarz, C., Lesnick, T., et al. 2020 in JAMA Network (Nedelska et al., 2019)

- We showed that Aβ accumulation longitudinally in DLB patients follows the similar trajectory that was demonstrated in AD patients before, including cognitively unimpaired adults who are at risk of cognitive decline. The trajectory of Aβ accumulation over time is like the sigmoid curve first proposed by Clifford Jack and his hypothetical model of temporal evolution of AD biomarkers. Thus, it appears that amyloid behaves quite uniformly in various neurodegenerative disorders, and its rates of accumulation first increase, then peak and then decrease towards a plateau. This has implications for designing clinical trials, and to consider anti-amyloid treatments for selected DLB patients as well.

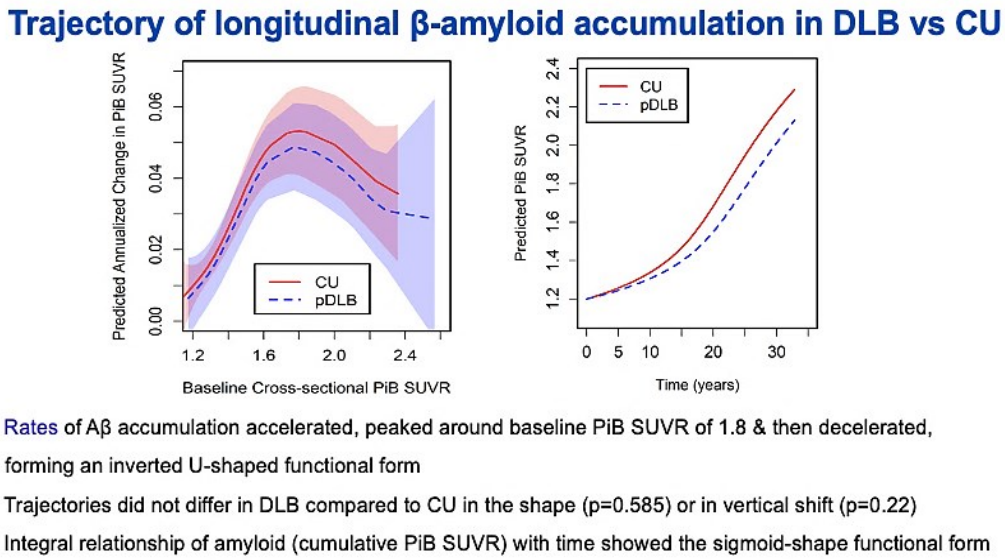
Background: In individuals with probable DLB, overlapping AD pathology is common and is associated with a faster decline and a shorter survival time. On amyloid PET with PiB tracer, more than half of patients with DLB show high Aβ levels; however, the trajectory of longitudinal Aβ accumulation over time and its associations with clinical and cognitive impairment in DLB remain unknown. **Our objectives were**: 1. to identify the trajectory of Aβ accumulation in individuals with probable DLB, 2. to investigate the relationships between Aβ accumulation and clinical and cognitive impairment in DLB over time; 3.to calculate sample size estimates for a hypothetical clinical anti-Aβ trial in DLB patients using decrease in rates of amyloid accumulation as an outcome measure compared to traditional outcome measures

Methods: This longitudinal cohort study compared n=35 consecutive patients with probable DLB from the Mayo Clinic ADRC with n=140 cognitively unimpaired (CU) volunteers from the population-based Mayo Clinic Study of Ageing matched on age, sex and APOE ε4 status to DLB patients. All received two serial Aβ PET with PiB tracer approximately two years apart to measure Aβ by PiB PET standardized uptake value ratio (SUVR) and comprehensive clinical and cognitive evaluations.

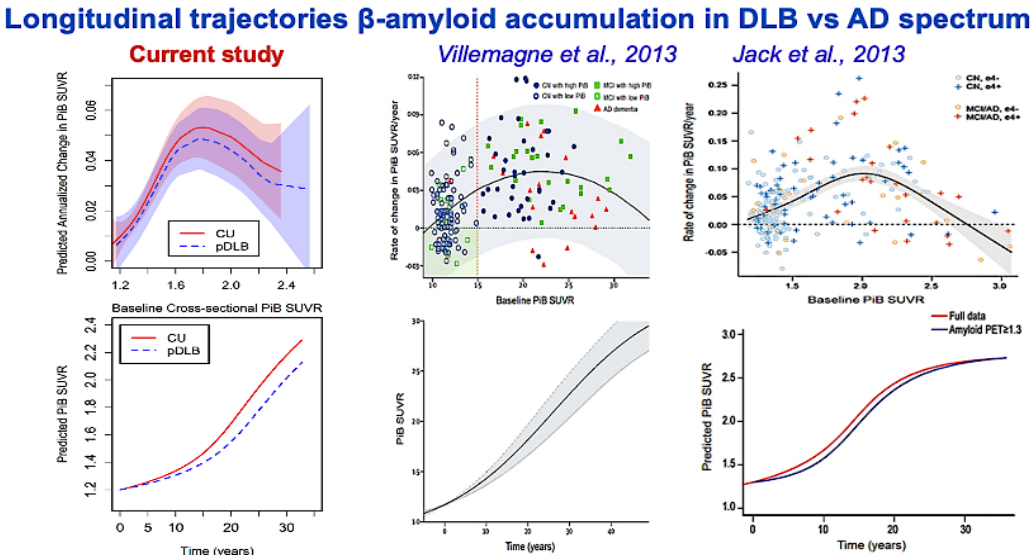
Results: A total of 175 individuals were assessed: n = 35 (20.0%) with probable DLB;mean age (SD), 69.6 (7.3) years. Of these, n = 16 (45.7 %) APOE ε4 carriers; n = 31 (88.6 %) males; and n = 140 (80.0%) CU adults; mean age, (SD) 69.7 (7.2) years; n = 64 (45.7%) APOE ε4 carriers; n = 124 (88.6%) males. In all groups, the rates of change in PiB SUVR

demonstrated an initial acceleration at lower baseline PiB SUVR values, followed by a slowing at higher baseline PiB SUVR values, thus forming an inverted U-shaped form of amyloid accumulation by baseline amyloid load.

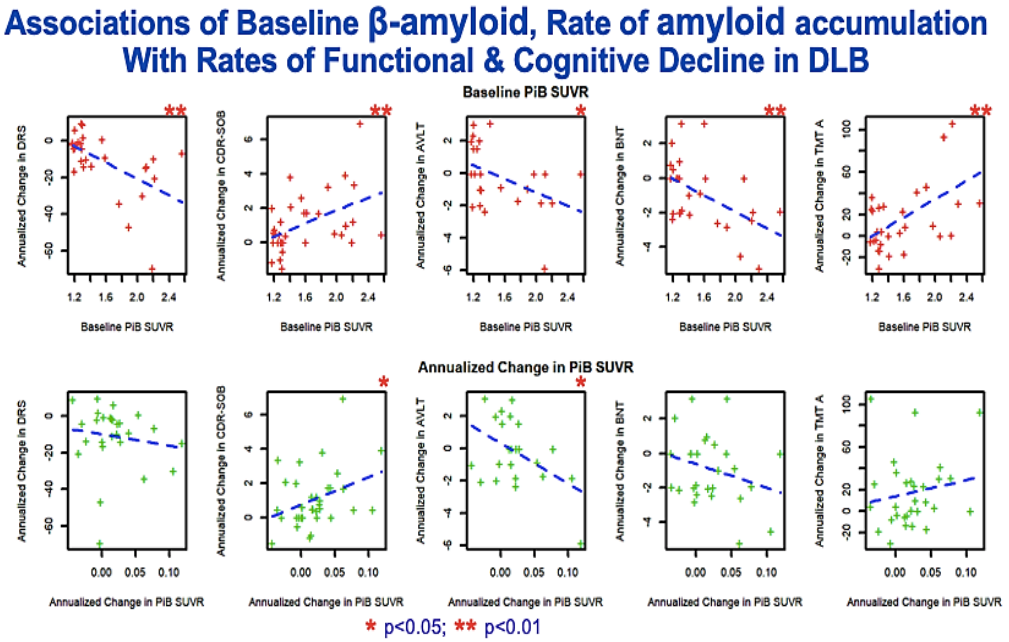
The trajectories of the rates of change in PiB SUVR did not differ in terms of shape (P =0.59) or vertical shift (coefficient [SE] 0.007 [0.006]; P = 0.22) between prodromal DLB and cognitively normal subjects. In both groups, the integral relationship between cumulative PiB SUVR and time in years had a sigmoid-shaped functional form. Both, a higher PiB SUVR at baseline cross-sectionally and change in PiB SUVR over time were associated with a more rapid clinical decline in probable DLB, as measured by the Clinical Dementia Rating, sum of boxes (baseline PiB SUVR: regression coefficient [SE], 1.90 [0.63]; P =0.005; R2 = 0.215; change in PiB SUVR: regression coefficient [SE], 16.17 [7.47]; P = 0.04; R2 = 0.124) and the memory Auditory Verbal Learning Test, delayed recall (baseline PiB SUVR: regression coefficient [SE], -2.09 [0.95]; P = 0.04; R2 = 0.182; change in PiB SUVR: regression coefficient [SE], -25.05 [10.04]; P = 0.02; R2 = 0.221)



Panel 1. Summarizes the predicted amyloid accumulation represented by the longitudinal change in PiB SUVR with respect to baseline amyloid accumulation, resulting in a U-shaped trajectory of amyloid accumulation (left). When this U-shaped trajectory is integrated into predicted amyloid over time in years, we get the sigmoid curve of longitudinal amyloid accumulation over years with a tendency to plateau with higher amyloid accumulation values. However, at the beginning of trajectory, amyloid accumulation is slow and protracted, and takes off later, around 15 years into the process. This sigmoid curve resembles amyloid accumulation curve in AD patients.



Panel 2. Emphasizes the current study findings in DLB (left column) when compared to other significant studies on longitudinal amyloid accumulation in AD continuum by Villemagne et al (Villemagne, Burnham, Bourgeat, Brown, Ellis, Salvado, Szoeke, Macaulay, Martins, Maruff, Ames, Rowe, & Masters, 2013), middle column and Jack et al.(Jack, Wiste, et al., 2013), right column. The similarity of amyloid accumulation curves in DLB and in AD (including prodromal and preclinical AD) is obvious.



Panel 3. summarizes the associations among baseline cross-sectional amyloid accumulation (top row) and longitudinal amyloid accumulation (bottom row) as predictors and longitudinal change in functional and cognitive tests or scales as outcomes. Higher baseline amyloid predicts worsening in all depicted cognitive and clinical tests over time. Faster amyloid accumulation over time is especially associated with overall functional and memory decline in DLB patients.

Sample size estimates for a hypothetical clinical trial in DLB

	12 months of follow-up		18 months of follow-up		24 months of follow-up	
Reduction in slope	25%	50%	25%	50%	25%	50%
PiB SUVR (size, CI)	**602 (521- 682)**	**151 (131 - 170)**	**258 (224 - 292)**	**65 (57 - 73)**	**151 (131 - 171)**	**38 (33 - 43)**
DRS (size, CI)	867 (735 - 1000)	215 (181 - 251)	370 (309 - 431)	94 (79 - 108)	218 (185 - 250)	55 (46 - 63)
CDR-SOB (size, CI)	768 (655 - 882)	193 (164 - 221)	328 (280 - 377)	83 (71 - 95)	193 (164 - 222)	49 (42 - 56)
MMSE (size, CI)	1583 (1262 - 1904)	397 (321 - 472)	681 (543 - 820)	170 (138 - 203)	395 (313 - 477)	99 (79 - 118)

- Subset of DLB patients may be considered as candidates for anti-amyloid treatments that currently include only patients within the AD continuum

p<0.05, 80% power; Sizes along with asymptotic confidence intervals are estimated using mixed-effects models as mean values using jack-knife resampling

Panel 4. Shows the sample size estimates for a trial in DLB patients that would be hypothetically targeted against amyloid, since we have shown earlier that amyloid accumulation in DLB and AD is similar, and that it results in clinical and cognitive decline in DLB. The sample estimates are calculated for various trial follow-ups with a 25 or 50 % effect size (amyloid reduction). It is shown that choosing slowing or reduction in amyloid accumulation or CDR-SOB functional test in DLB patients as outcome measure would require the smallest sample sizes (as opposed to traditional MMSE or DRS in trials in AD patients).

Conclusion: In this study, the rate of change in PiB SUVR among patients with probable DLB increased, peaked, and subsequently decreased in a trajectory comparable to that of cognitively normal adults and the trajectory known from the AD continuum. Higher baseline PiB SUVR and PiB SUVR change over time were associated with a faster clinical and cognitive deterioration over time. Measurement of the change in PiB SUVR over time has implications for the design of potential anti-amyloid randomized clinical trials for DLB patients in the future.

4.3.5. Study IX: Longitudinal atrophy in prodromal dementia with Lewy bodies points to cholinergic degeneration

Published in Kantarci, K.*, and **Nedelska, Z.***, Chen, Q., et al., 2022 in Brain Communications (Kantarci et al., 2022)

- We showed a significant baseline atrophy of cholinergic nucleus basalis of Meynert in patients with prodromal DLB, and that longitudinal rates of regional cortical atrophy affect especially regions reported to receive the densest cholinergic inputs from nucleus basalis of Meynert. This cholinergic atrophy occurs early on during the course of DLB and is present also in autopsy-verified patients.

Background: Mild cognitive impairment displaying the core clinical characteristics of dementia with Lewy bodies is regarded as the prodromal stage of dementia with Lewy bodies (MCI-LB). Although some atrophy of grey matter has been reported in prodromal dementia with Lewy bodies, longitudinal rates of atrophy, especially in those who progress to probable dementia with Lewy bodies remain unclear.

Objectives of this study were two-fold: 1. to investigate the regional patterns of both cross-sectional and longitudinal rates of grey matter atrophy in patients with prodromal dementia with Lewy bodies, including those who progressed to probable dementia with Lewy bodies and those who had autopsy-confirmed diagnosis compared to cognitively intact age- and sex-matched controls; and 2. to assess whether greater rates of atrophy, and where, are associated with clinical progression or cognitive decline over time in prodromal dementia with Lewy bodies.

Methods: Included were patients with mild cognitive impairment and at least one core clinical feature of dementia with Lewy bodies (n = 56, mean age = 70.5, 95% males), who were recruited in the Mayo Clinic ADRC and followed for at least two clinical assessments and MRI scans. A cognitively normal control group (n = 112) was matched to patients with MCI-LB on age and sex in a ratio of 2:1. MCI-LB patients either remained stable (n = 28) or progressed to probable dementia with Lewy bodies (n = 28) throughout a comparable follow-up period, with pathologic confirmation available in a subset of cases (n = 18). Using both, voxel-based (for the pattern) and atlas-based region of interest analysis (for the magnitude of change), cross-sectional and longitudinal rates of grey matter atrophy were determined.

Results: Prodromal dementia with Lewy bodies (MCI-LB) was defined at baseline by a

profound cross-sectional atrophy in the cholinergic basal forebrain (nucleus basalis of Meynert) in both those who remained stable and those who progressed to probable dementia with Lewy bodies ($p < 0.05$, false discovery rate adjusted). The greatest longitudinal rates of atrophy were observed in the entorhinal and parahippocampal cortices, temporoparietal association cortices, thalamus, and the basal ganglia in patients with mild cognitive impairment who progressed to probable dementia with Lewy bodies at follow-up ($p < 0.05$, false discovery rate corrected). Greater rates of disease progression by the clinical dementia rating-sum of boxes were associated with higher rates of cortical atrophy in temporal cortices. Seventeen of the eighteen (94 %) of autopsied patients had Lewy body disease at autopsy, and these also displayed pattern of profound cholinergic basal forebrain atrophy at the baseline.

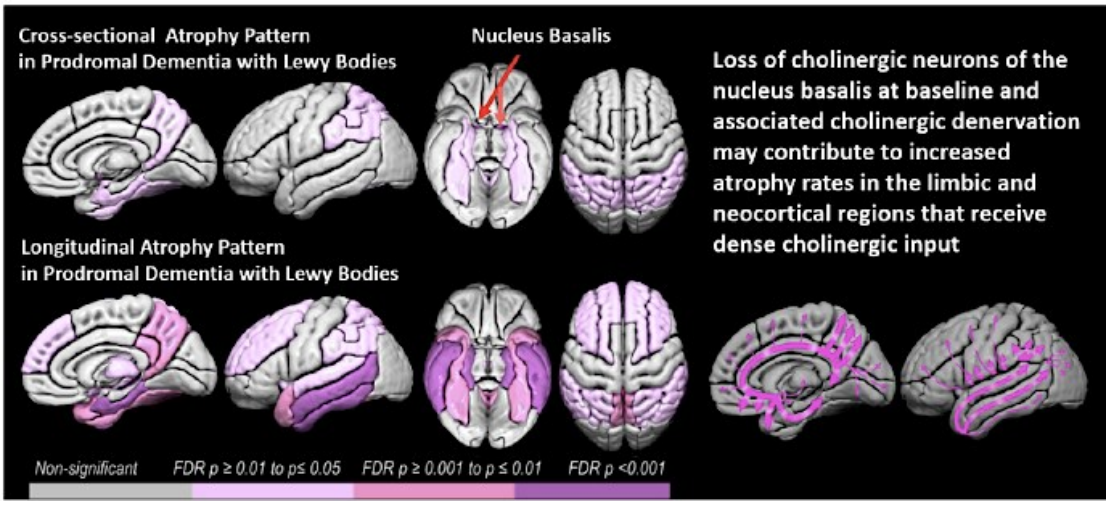


Figure 31. summarizes the main findings of the study, showing that prodromal DLB (MCI with core LB features) is characterized by relatively circumscribed atrophy at baseline (top row), especially in the cholinergic nucleus basalis of Meynert and temporoparietal cortices (pink shades). The longitudinal rates of atrophy (bottom row) are more pronounced (purple shades) and wide-spread compared to looking at a single cross-sectional time-point and the atrophy over time occurs in all ot the cortical regions that receive dense cholinergic inputs from nucleus basalis of Meynert (Kantarci et al., 2022).

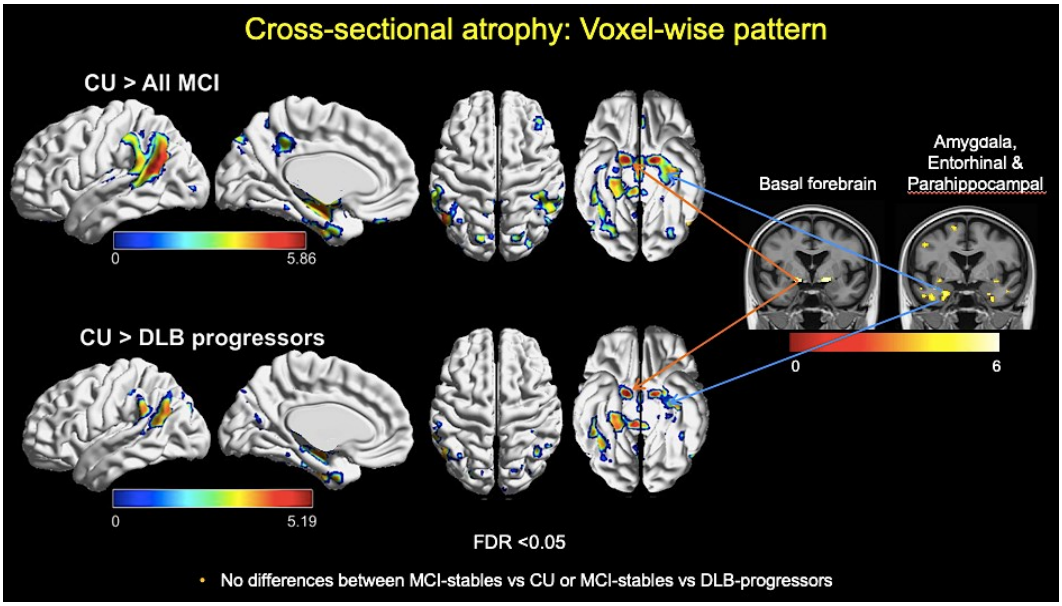


Figure 32. shows the pattern and the magnitude of the baseline (cross-sectional) atrophy in prodromal DLB (all MCI-LB including those who remained stable over time and who progressed to full blown DLB, top row), and in those prodromal DLB who later progressed to full blown DLB (bottom row) compared to the normal controls. The atrophy pattern in prodromal DLB includes basal cholinergic forebrain, amygdala, entorhinal and parahippocampal cortices, and parietotemporal cortices.

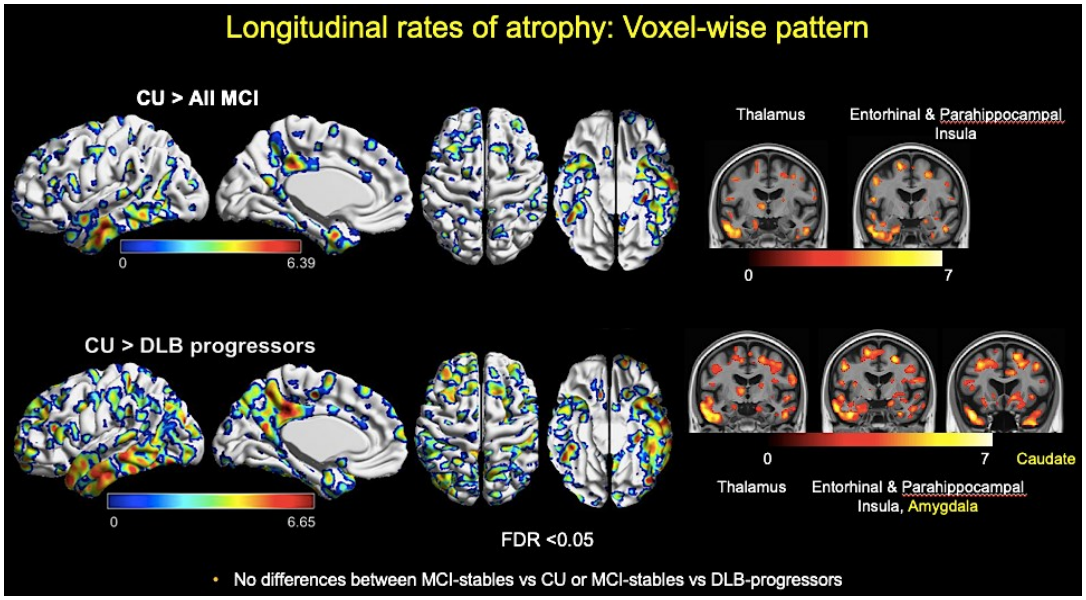


Figure 33. shows the pattern and the magnitude of the rates of atrophy over the time in prodromal DLB (all MCI-LB including those who remained stable over time and who progressed to full blown DLB, top row), and in those prodromal DLB who later progressed to full blown DLB (bottom row) compared to the normal controls. The rates of atrophy reveal the wide-spread atrophy pattern in prodromal DLB which again includes basal cholinergic forebrain, amygdala, entorhinal and parahippocampal cortices, but also thalamus and wide-spread cortical regions.

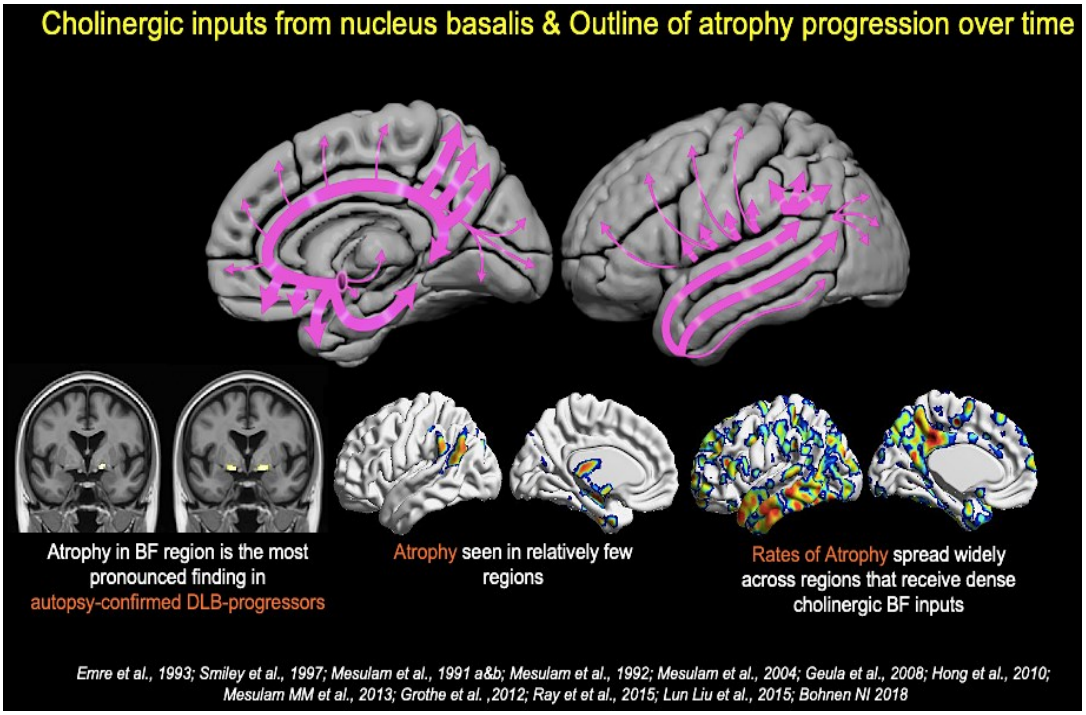


Figure 34. is a schematic representation of the cholinergic nucleus basalis of Maynert (pink circle in the basal forebrain area) and the cholinergic projections and their presumed strength into almost all cortical regions. Bottom row (lef) shows that in a subset of DLB patients who were followed up longitudinally antemortem, died later and had LB at autopsy, the atrophy in nucleus basalis of Meynert was truly the prominent and almost the sole region that was atrophied (other regions did not show up perhaps to a smaller sample size of autopsied patients). Middle figure again emphasizes relatively small and circumscribed pattern of cross-sectional atrophy in prodromal DLB, however, when we look at atrophy in prodromal DLB from a longitudinal perspective, we see wide-spread atrophy, in regions that receive cholinergic supply from nucleus basalis of Meynert (almost all cortical regions are affected, right panel).

Conclusion: Results indicate that atrophy in the nucleus basalis of Meynert is a characteristic of prodromal dementia with Lewy bodies occurring early on during disease, irrespective of the proximity to clinical progression to probable dementia with Lewy bodies. Longitudinally, grey matter atrophy proceeds in areas with strong cholinergic innervation, in accordance with clinical disease development, with extensive and rapid atrophy rates in individuals who advance to probable dementia with Lewy bodies. Patients with prodromal dementia with Lewy bodies are the candidates for cholinesterase inhibitor therapy due to the substantial neurodegeneration in the cholinergic system. Formally, this therapy has been reserved to AD patients so far but not prodromal DLB patients.

4.3.6. Study X: Cerebrovascular disease, neurodegeneration, and clinical phenotype in dementia with Lewy bodies

Published in Ferreira, D., **Nedelska, Z.**, Graff-Radford, J., et al., 2021 in Neurobiology of Ageing (Ferreira et al., 2021)

- We showed that white matter hyperintensities and infarcts are common cerebrovascular lesions in DLB, are associated with regional cortical atrophy, and can influence clinical phenotype in DLB. We suggested pathophysiological mechanisms how can WMH contribute to cognitive impairment.

Background: In this study, we investigated the role of cerebrovascular disease using various vascular-related imaging findings in the progression of neurodegeneration and in the clinical phenotype of patients with DLB. The previous studies on cerebrovascular pathology in clinically probable DLB were sparse and inconclusive as to whether and how these pathologies relate to cognitive decline.

Methods: Using structural magnetic resonance imaging, we measured the regional cortical thickness and subcortical grey matter volumes of n = 165 individuals diagnosed with probable DLB recruited from the multisite international observational longitudinal study the European Dementia with Lewy Bodies consortium and from the Mayo Clinic ADRC. Cortical and subcortical infarcts were counted by a single expert, and white matter hyperintensities (WMH) were assessed by the expert semi-quantitatively using a novel, user-friendly visual rating scale derived from training dataset of quantitatively measured white matter hyperintensities in all DLB patients.

Results: WHM were common finding in DLB patients, although often mild to moderate in their severity. Infarcts were present in almost one fifth of the participants. Subcortical infarcts alone were found to be more common (13.3%) than either cortical infarcts alone (3.1%) or a combination of subcortical and cortical infarcts (2.4%). Infarcts were associated with WMH, and this association was significant regardless of the kind of infarct. A larger volume of the WMH was associated with thinner cortices in the orbitofrontal, retrosplenial, and posterior cingulate regions, as well as a smaller volume of thalamus and pallidum, and a larger volume of the caudate. There was a correlation between a higher WMH volume and the presence of visual hallucinations, as well as lower global cognitive performance, and a trend towards the absence of probable rapid eye movement sleep behaviour disorder. There was a correlation between the presence of infarcts and the absence of parkinsonism. Furthermore, significant proportion of WMH co-localized to or around cholinergic cingulate

pathway that provides inputs to several cortical regions, suggesting the possible mechanism of WMH contribution to cognitive decline.

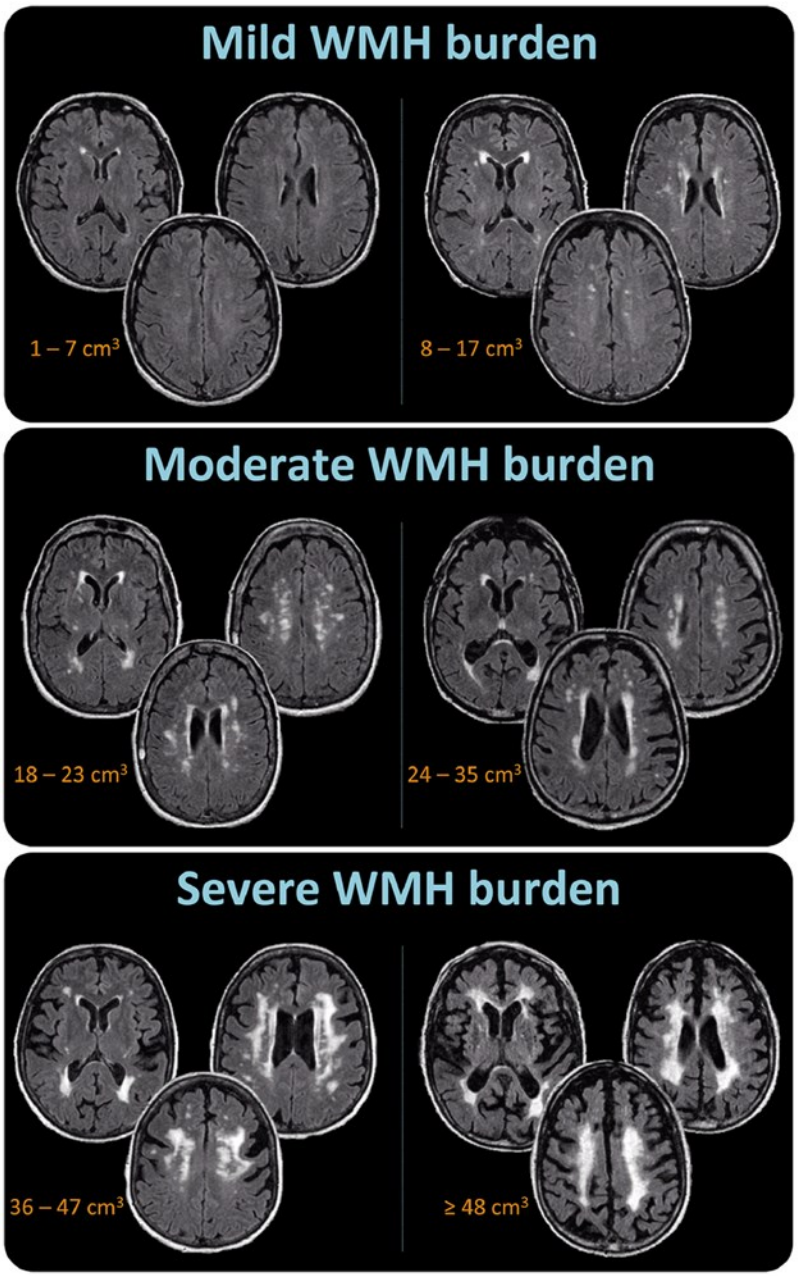


Figure 35. shows the semiquantitative rating of mild (top), moderate (middle) and severe burden (bottom) of the white matter hyperintensities (represented as WMH volume in cm^3) as one of the measures of cerebrovascular disease in multinational multisite cohort of DLB patients (Ferreira et al., 2021). To design each category of the three-stage visual grading scale for WMH, the two quantitative WMH volume categories were combined: 1-17 cm3 of WMH for mild burden, 18-35 cm3 for moderate burden and over 36 cm3 for severe WMH burden.

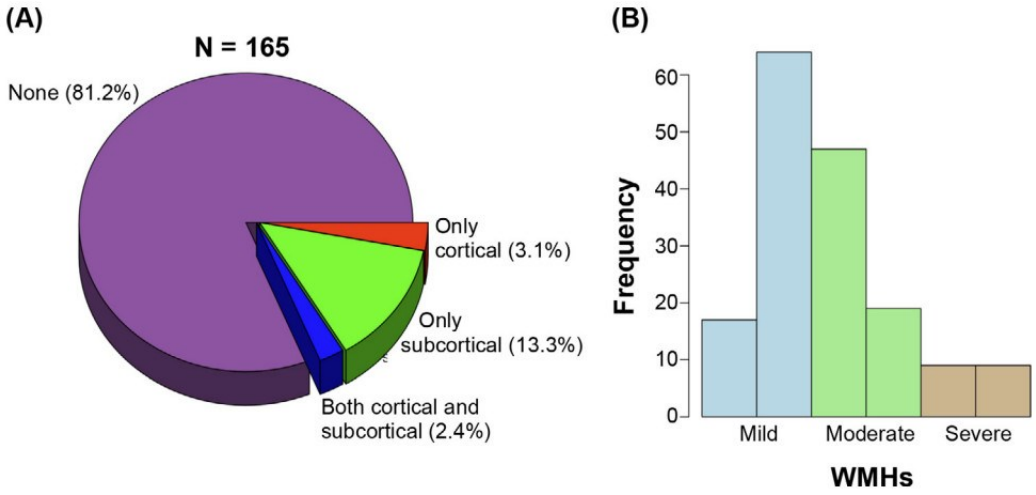


Figure 36. shows the pie chart (A) summarizing the proportions of various distributions of visually rated infarcts within the whole multinational DLB cohort showing that almost 19% of DLB patients have cerebral infarcts typically in a subcortical localization; and (B) colour-coded frequencies of WHM severity showing that severity of WMH as a measure of small vessel disease is most often relatively mild to moderate in DLB patients (Ferreira et al., 2021).

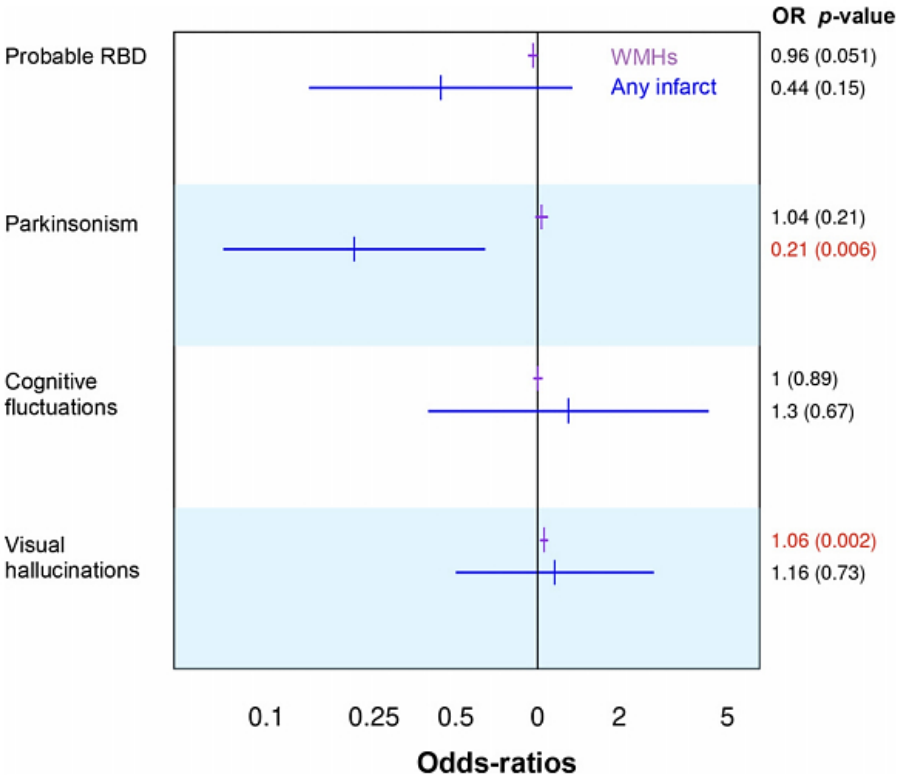


Figure 37. shows the associations among various cerebrovascular pathologies, WMH or infarcts, and their associations with the DLB core clinical features expressed as odds-ratios (Ferreira et al., 2021). Higher WMH burden is significantly associated with a higher frequency of visual hallucinations and lower frequency of RBD (trend). More infarct, interestingly, were associated with lower frequency of parkinsonism.

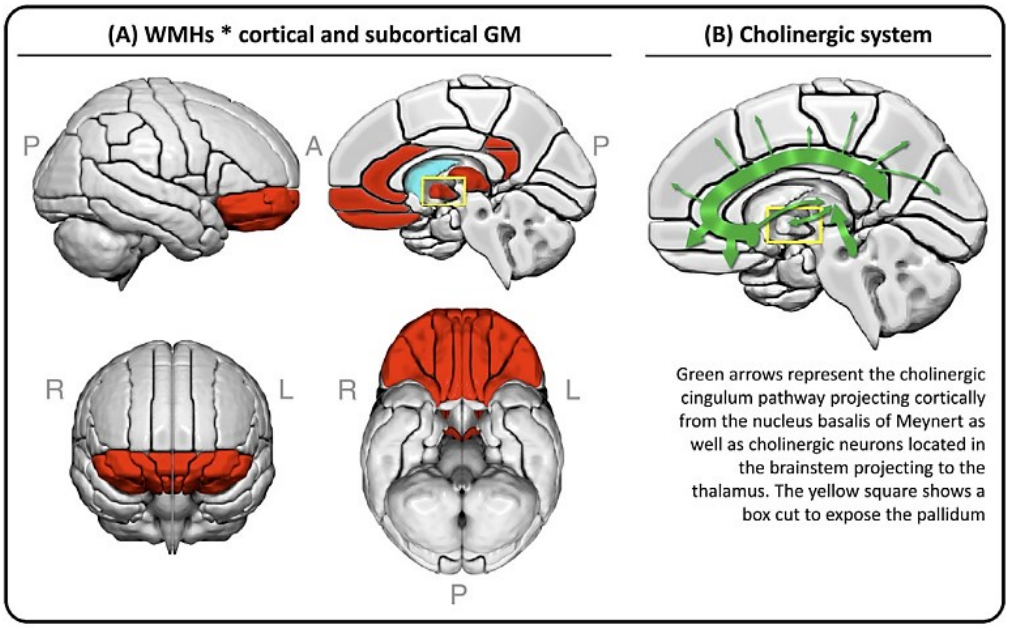


Figure 38. is mapping the associations between WMH burden and cortical regional grey matter atrophy (A; significant associations are red coloured, including subcortical pallidum). The WHM are, interestingly, co-localized to the regions where the cingulum cholinergic pathway is located and that provides dense cholinergic inputs to several cortical regions from nucleus basalis of Meynert (B); this strategic localization of WMH could possibly be one of the underlying mechanisms of how WMH contribute to cognitive decline in DLB (Ferreira et al., 2021).

Conclusion: The presence of infarcts and WMH tend to obscure the typical clinical features of DLB such as rapid eye movement sleep behaviour disorder or typical parkinsonism but can contribute to manifested visual hallucinations. This might have repercussions for the comprehensive management and treatment of DLB patients including treatment of their cerebrovascular disease and related modifiable factors.

5. Discussion, conclusions, and potential application of our findings

5.1. The spatial navigation tests are highly relevant to AD pathophysiology

In our Study I., we demonstrated that the impairment of the world-centred (allocentric) spatial navigation (SN) strategy is associated with the atrophy of right hippocampus, both in a real space and in the two-dimensional computer representation of a real space. This association was observed across the AD continuum, but was strong especially in patients with MCI and full-blown AD dementia. Right hippocampal atrophy played a crucial role in the allocentric SN impairment even when accounting for the whole brain atrophy and left hippocampal atrophy and when controlling for standard demographic variables. Our study findings of the right hippocampus as a key player in the allocentric SN are aligned with those performed in animals (Morris et al., 1982) and humans (Astur et al., 2002; Burgess et al., 1998), however, the previous studies did not study individuals with AD.

We found the same pattern of association between right hippocampal atrophy and allocentric SN impairment in both, the real-world and computerized versions of SN tests. Even though the computer 2D version may not entirely replace the real-space setting, our study demonstrates that the relatively easy-to-administer and cheap computer-based SN test can be used to clinically and functionally examine individuals with hippocampal dysfunction in early AD (Hort et al., 2007).

5.2. Spatial navigation testing provides a unique information about patients at risk of AD above and beyond traditional neuropsychology

In our Study III. we used a data reduction technique (factor analysis) to test associations between established cognitive functions (domains) and SN and between SN, memory scores, and hippocampal atrophy; all these known markers of AD pathophysiology. Because the SN is a complex skill and behavior we aimed at showing that SN can be distinguished from other cognitive functions and domains. Utilizing our real-space version of SN test, we indeed showed that allocentric and egocentric SN scores loaded on a component distinct from six established cognitive processes such as verbal and nonverbal memory, executive, and visuospatial function, attention/working memory, and language, i.e. they were not intercorrelated with each other. Consequently, we concluded that SN and other traditional cognitive domains share only a modest variance.

Additionally, we showed that there was no association between SN performance and performance on any well-established cognitive function among the cognitively normal older individuals. For those with amnestic MCI (which progresses to AD dementia most often),

only executive function was associated with allocentric SN, whereas verbal memory was associated with egocentric navigation. However, these associations only explained a small fraction of the variance in the SN (11 % and 9%, respectively). In individuals with amnestic MCI, however, both left and right hippocampal volumes were associated with allocentric SN and explained 12 % and 26%, respectively, of the variance in allocentric SN, controlling for age, sex, and education.

Our findings imply that SN can be separated from other cognitive functions. In a previous study by our team (Hort et al., 2007) we demonstrated already that allocentric SN impairment occurs early on during AD at the stage of MCI, that our SN tests can distinguish amnestic vs nonammestic MCI (Laczo et al., 2009) and that the right hippocampus is crucial for allocentric SN (Nedelska et al., 2012). Alltogether, SN evaluation is useful and beneficial in characterizing both the cognitive and clinical/functional performance in older adults, particularly those at risk for AD. Our findings can serve as a foundation for the future study aimed at adressing the earliest symptoms in preclinical and prodromal AD and tracking the progression of AD.

5.3. Prosody as an important social skill is impaired in AD

In our Study II targeted at understanding of the social and communication impairment in AD and its anatomical correlations using brain volumetry, we examined whether patients with amnestic MCI due to AD and those with full-blown AD dementia manifest an abnormal emotional prosody recognition (EPR) from voice compared to cognitively normal peers. We measured the associations of EPR scores with brain volumes and cortical thickness of regions associated with emotional processing such as amygdala, temporal pole (Olson et al., 2007), rostral and caudal anterior cingulate, superior temporal sulcus (Watson et al., 2014), with respect to a global cognitive status approximated by MMSE score. We demonstrated that prodromal AD and full-blown AD patients have diminished EPR skills compared to normal older peers (Bush et al., 2000). Patients with AD dementia have EPR even more impaired than prodromal AD patients, controlling for age and education. EPR score moderately/strongly correlated with caudal anterior cingulate thickness, with temporal pole volume and with superior temporal sulcus thickness, the structures known to be associated with emotional processing but also AD progression. Discrimination analysis by ROC demonstrated a good sensitivity of EPR as a tool to distinguish between controls vs patients (AD dementia and prodromal AD combined), controls vs prodromal AD, and even between prodromal AD patients and those with AD dementia. Thus, EPR could provide an additional

tool for AD stageing targeted at social and communication skills that are not typically included in neuropsychological evaluations, but are relevant to every-day functioning (Hasson-Ohayon et al., 2017). Our findings could inform the future studies aiming at social management and relief to patients with AD and their caregivers.

5.4. Non-invasive and widely available technique MR spectroscopy can predict the future amyloid accumulation over time in clinically normal adults at risk of AD

In cross-sectional amyloid PET studies, 20–40 % of older adults who are still clinically normal (CN) show a considerable amyloid load on PET (Jack et al., 2014; Jansen et al., 2015; Rowe et al., 2010). Individuals with a greater amyloid accumulation may be more vulnerable to MCI (Villemagne et al., 2011) and progression to dementia in the future (Leal et al., 2017). However, it is not feasible to scan everyone with amyloid PET, a relatively expensive, invasive and technically demanding procedure. Cheaper and more accesible markers of amyloid accumulation, such as those associated with MRI, are required.

In our Study V., using a large population-based sample of 594 cognitively unimpaired older adults, we demonstrated that a noninvasive and affordable measurement of selected brain metabolites at baseline by MRS, a common MRI techniqe, is predictive of a higher rate of amyloid accumulation on serial PET in the near future. Taking into consideration age at baseline, sex, and APOE4 status, we showed that a lower baseline ratio of brain metabolites N-acetylaspartate to myoinositol (NAA/mI, a composite marker of neuronal viability and synaptic integrity) and a greater myoinositol to creatine ratio (mI/Cr, a marker of glial activation and inflammation) were associated with a higher rate of amyloid accumulation. Furthermore, amyloid accumulated more rapidly in APOE4 cognitively unimpaired carriers compared to APOE4 non-carriers. This was the first study to confirm APOE4 effects on rates of amyloid accumulation over time in clinically yet normal participants.

APOE4 status had, however, no effect on the association between baseline metabolite levels and the rate of amyloid accumulation. Both, MRS metabolites and APOE4 are likely independently related to an increased amyloid accumulation over time.

The future studies should address the standardization and harmonization procedures for multi-site MRS acquisition. Furher, a longitudinal MRS studies should provide a necessary information on the temporal sequence of MRS metabolites vs amyloid accumulation.

5.5. DLB: necessity for multimodality imaging

In the third aim of this disseration, I have worked on multiple imaging studies trying to

understand the LB-related pathophysiology as it develops from prodromal to full blown DLB. How to disentangle the LB-related and AD-related contributions to image findings, and how the overlapping LB and AD-related pathology affects the clinical phenotype of DLB patients.

Previous studies suggested relative sparing of MTL structures on MRI in DLB compared to AD (Ballmaier et al., 2004; Burton et al., 2002), where MTL atrophy is one of hallmark signs (Jack et al., 2002). However, other studies reported similar MTL atrophy between groups, likely due to involvement of DLB patients with mixed atrophy. The autopsy-confirmed study with patients followed up longitudinally to record their clinical progression, was missing. In our study V (Nedelska, Ferman, et al., 2015) we determined that patients with pathologically „pure" LB who were premortem diagnosed as having DLB indeed had lower brain atrophy rates globally and in amygdala and hippocampus, and were similar to controls. However, patients with pathologically mixed DLB with AD had significant rates of atrophy globally and in MTL structures, similar to patients with „pure" AD. Those DLB with mixed pathology progressed faster and cognitively declined faster, confirming previous reports on more aggressive disease progression in (mixed) DLB (Lemstra et al., 2017; Rongve et al., 2014) in an unique longitudinal cohort with autopsy confirmation. The finidings of this study helped to establish the relative preservation on MTL structures on MRI in DLB as supportive clinical marker in the Fourth report of DLB consortium criteria for diagnosis and management of DLB (McKeith et al., 2017).

White matter (WM) of the brain has been less investigated in DLB patients, and previous findings showed equivocal findings of wide-spread patterns of impaired microintegrity of WM (Watson et al., 2012) to less prominent and focal findings in the WM of limbic structures and inferior longitudinal fascicle (Kantarci et al., 2010) which was associated with presence of visual hallucinations in DLB. It has been unknown whether and how the WM microstructure is affected by overlapping AD pathology in DLB, and this could contribute to the discrepancies in previous studies. Thus, in our next study VI. (Nedelska, Schwarz, et al., 2015) we used DTI, FDG PET and amyloid PET to measure the effect of AD pathology on WM microstructure and to contrast the WM findings with changes in adjacent cerebral cortex in DLB. We showed a relatively well circumscribed region of white matter, bordering posterior parietal, occipital and temporal lobe. This region was relatively small, but this part of WM has been an important „cross-roads" as both superior and inferior longitudinal fascicles pass through this WM, and are implicated in „what" and „where" complex information processing (Mesulam, 1998). Indeed, we observed a borderline association

between impaired microstructure in this region and cognitive fluctuations and visual hallucinations in DLB patients, likely to relatively smaller groups. Furthermore, amyloid load on PET did not affect this focal WM finding, which is specific to DLB. Finally, we showed that WM impairment closely overlapped with glucose metabolism in adjacent parts of cerebral cortex, which can further contribute to pathophysiology of cognitive fluctuations and visual hallucinations in DLB.

Another, a well-established, imaging finding associated with DLB has been cingulate island sign, CIS (Lim et al., 2009), a supportive imaging biomarker of DLB. The CIS sign has been derived from FDG-PET which is relatively less available and more invasive method compared to MRI. Because the brain glucose metabolism is tightly coupled with blood perfusion, we used noninvasive perfusion MRI technique to investigate CIS and cortical perfusion patterns in DLB in our study VII. We showed an excellent correlation between FDG PET and perfusion MRI for the CIS and regional perfusion-metabolism patterns. CIS from perfusion MRI could distinguish AD from DLB with accuracy over 80 % even when proportion of DLB patients did have overlapping AD pathology. We also confirmed our hypothesis that when AD pathology is present, which we examined using tau-PET meta-ROI derived from medial temporal regions typical for AD, the CIS was decreasing. Lower perfusion in CIS components was associated with worse global cognitive scores. We suggest that perfusion MRI as more affordable, less invasive and more available alternative to DLB biomarker ascertainment when FDG PET is not available.

In our next study VIII, we established for the first time the trajectory of amyloid accumulation in DLB over time using serial amyloid PET (Nedelska et al., 2019) as a function of baseline amyloid load and as a function of time. The amyloid accumulation curve showed a sigmoid shape, with initial slow accumulation, followed by an acceleration and with subsequent plateau. This curve in DLB was similar to amyloid accumulation curve in AD continuum (Jack, Wiste, et al., 2013; Villemagne et al., 2011). Moreover, amyloid accumulation was associated with longitudinal functional decline and cognitive worsnening in DLB patients, whereas previous, cross-sectional studies were not able to provide unequivocal findings on amyloid vs cognition relationship in DLB (Donaghy et al., 2013). Our study has two other major conclusions: at least subset of DLB patients could benefit from emerging antiamyloid drugs in the future which are currently reserved to AD patients. Our sigmoid shape od amyloid accumulation in DLB informs that such antiamyloid trial in DLB would be the most effective early on before the amyloid accumulation accelerates, similar to dynamics and intervention planning in AD. We also calculated sample sizes for

such hypothetical antiamyloid trial in DLB, and we showed that using reduction in amyloid SUVR as outcome measure, and using CDR SOB scale as another potential outcome measure as opposed to more traditional MMSE or DRS would help to plan the trial design, reduce the needed sample size, reduce the costs and potentially increase the success of such trial by utilizing functional measures that adress the fucntional status in DLB better than other measures that are primarily designed for AD patients.

Because the need for early diagnosis and management in DLB shifts research to prodromal stages, mirroring the development in AD field, a lot of effort is placed into characterizing prodromal DLB stages and biomarkers associated with it. This effort culminated in research criteria for prodromal DLB diagnosis (McKeith et al., 2020). REM sleeep behaviour disorder, myocardial MIBG, DaTscan and quantitative EEG play an important role in prodromal DLB diagnosis, with structrual MRI and molecular imaging also being important as tools to ascertain overlapping AD pathology in DLB. However, more research is needed to understand the longitudinal evolution of these biomarkers during the prodromal stage.

Thus, in our study IX (Kantarci et al., 2022), we investigatated the baseline cross-sectional and longitudinal regional atrophy and rates of atrophy in MCI patients with core LB features, some of them deceased and autopsy-confirmed as having LB. We showed that cholinergic system, namely the nucleus basalis of Meynert is atrophied early on, and that pattern of atrophy in other brain regions maps with cholinergic outputs of this nucleus. Further, while cross-sectional regional atrophy is more focal and located to MTL, likely also due to some degree of AD intermixed pathology, longitudinal rates reveal a wide-spread atrophy pattern across wast cortical region that receive cholinergic inputs from nucleus basalis of Meynert. Our findings have implications for understanding the early, prodromal stages of DLB and support an administration of AChEI to DLB patients early on in MCI stage, whereas the insurance companies allow the administration only in full-blown dementia stage, arguing by non-existent randomized clinical trials in MCI due to LBD.

Finally, cerebrovascular disease in patients with DLB is clinically highly relevant, but little researched topic. In our last study presented in this dissertation (Ferreira et al., 2021) we demonstrated in a large multi-site and multinational cohort of DLB patients that white matter hyperintensities on MRI as a proxy of small vessel disease and cerebral infarcts, especially subcortical, are frequent findings in DLB patients, and their presence can obscure some of the core DLB features, which can make diagnosis more challenging. These cerebrovascular pathologies, however, are associated with a worse cognition and regional brain atrophy in DLB. Thus, it is important to address and clinically manage cerebrovascular disease in DLB.

6. Conclusion

The main overarching goal of this thesis was to study associations of morphometric and metabolic changes in brain structure and function with clinical and cognitive impairment in Alzheimer's disease dementia and dementia with Lewy bodies. Multimodality imaging was used to address various pathophysiologies developing in patients' brains of from different perspectives, including structural, microstructural and perfusion MRI and molecular methods measuring the accumulation of amyloid and tau-related pathophysiology by PET. Our first goal was to evaluate cognition, behaviour and functioning from a different perspective that are traditional pencil-and-paper-based neuropsychological tests. We utilized used more experimental and experiential examinations of spatial navigation and social and emotional cognition – the skills needed in every-day life and functioning which are not systematically evaluated in patients with cognitive impairment in clinical or even in research settings. However, to evaluate the cognitive profile of our patients and volunteers from a standard perspective of well-established cognitive domains, neuropsychological examinations were administered.

Because current research is heavily oriented at prodromal and preclinical stages of dementia, in our second aim, using the widely available brain MR spectroscopy to measure specific brain metabolites, we predicted the increase in brain amyloid accumulation in the near future in clinically yet unimpaired older participants who may be at increased risk of developing cognitive impairment and dementia due to AD.

In our third aim, we used an array of typically multimodality imaging evaluations to better understand the pathophysiology of dementia with Lewy bodies where AD-related pathophysiology frequently overlaps with LB which has negative repercussions for patients and their caretakers in terms of faster progression and shorter survival.

The multitude of our findings confirm the indispensable contribution of brain imaging methods in our understanding of Alzheimer-related and Lewy body related pathophysiology and associated clinical, cognitive, and behavioural impairment.

7. Summary

Alzheimer's disease (AD) represent a burden to patients, caregivers and society. Reliable and affordable tests and biomarkers aiming at early diagnosis are necessary for effective interventions and therapies. Except for cognitive symptoms classified into traditional cognitive domains, other difficulties arise in daily lives of AD patients such as impaired spatial navigation or poorer social and nonverbal communication skills putting further strain on patients and their daily functioning. Relatively little research has been conducted utilizing tests validated by plausible anatomical associations at various AD stages. Using human analogue of Morris water maze, we showed that the right hippocampus is necessary for world-centred, allocentric spatial navigation, particularly in context of cognitive impairment due to with AD. Because hippocampal atrophy is well-established imaging biomarker of early AD, the spatial navigation tests could be used as affordable and reproducible enrichment to standard neuropsychology testing. We showed that spatial navigation is a unique skill or cognitive process that can be separated from the traditional cognitive domains. Further, using tests of emotional prosody recognition from voice, we demonstrated the step-wise impairment of this skill from prodromal to full-blown AD patients, associated with brain atrophy of structures relevant both for emotional processing and AD pathophysiology. The emotional prosody recognition test distinguished controls from MCI due to AD and MCI from AD dementia patients with a good accuracy. From anatomical structure-function associations, I moved to AD molecular imaging using amyloid PET, a well-established biomarker of amyloid pathology in vivo. Because the interventions are the most efficacious in early stages of AD, it is imperative to identify the preclinical and prodromal individuals at highest risk of cognitive decline. Amyloid PET is relatively expensive and not widely available. We showed that measurement of selected brain metabolites using non-invasive and available MR spectroscopy technique can predict the accelerated amyloid accumulation on PET in the near future in cognitively still unimpaired individuals. We also mathematically derived the trajectory of amyloid accumulation in DLB participants from the longitudinal amyloid PET for the first time and demonstrated that amyloid trajectory in DLB is similar to AD and is associated with clinical and cognitive decline in DLB. We also provided sample size estimates for an anti-amyloid trial in DLB because our data suggested that at least some DLB patients may benefit from anti-amyloid treatments. Using a multimodality imaging in DLB, we contributed to understanding of Lewy body-related pathophysiology and how frequently overlapping AD can modify the phenotype, prognosis and survival of DLB patients.

8. Souhrn

Alzheimerova choroba (AD) představuje závažnou zdravotnicko-společenskou výzvu. K včasné diagnóze AD a účinné léčbě potřebujeme spolehlivé a ekonomicky přijatelné diagnostické nástroje. Prostorová navigace a neverbální komunikace rozeznáváním různých modalit emocí jsou dovednosti nezbytné ke každodennímu životu; u pacientů s AD bývají narušené, a věnuje se jim méně pozornosti, protože nejsou dostupné validní testy. S použitím lidské analogie Morrisova vodního bludiště jsme ukázali, že pravý hipokampus je nezbytný pro allocentrickou prostorovou navigaci, zejména u osob s mírnou kognitivní poruchou a AD demencí. Protože hipokampální atrofie je již zavedeným biomarkerem AD, prostorové testy by mohly být relativně levnou možností, jak obohatit testování kognitivních funkcí u AD a dalších neurodegenerací. Navíc jsme prokázali, že prostorová navigace je unikátní kognitivní doména, do značné míry nezávislá na ostatních kognitivních funkcích testovaných běžnými neuropsychologickými testy. V další studii jsme ukázali poruchu emoční hlasové prozódie v prodromálním stádiu AD i pacientů s AD demencí, přičemž skór testu prozódie koreloval s atrofií mozkových struktur důležitých jak pro zpracování emocí, tak i pro AD. Podle skóru testu prozódie bylo možné odlišit prodromální AD od kontrol i od pacientů s již rozvinutou AD demencí. V další práci jsem se zabývala molekulárním zobrazením amyloidu pomocí PET, etablovaného in vivo biomarkeru AD. Kvůli plánování účinných intervencí potřebujeme cílit na osoby s preklinickou AD a snažit se najít způsob, jak rozpoznat ty, kteří se opravdu zhorší kognitivně, až do obrazu AD demence. S tím souvisí rychlejší ukládání amyloidu v čase, nejen jeho absolutní ukládání. Amyloidový PET je však relativně drahý, a ne všude dostupný. Pomocí dostupné a neinvazivní MR spektroskopie jsme změřili hladiny mozkových metabolitů, z nichž některé predikují rychlejší ukládání amyloidu v mozku v blízké budoucnosti u zatím kognitivně nepostižených seniorů. Dále jsme pomocí longitudinálního amyloidového PET vůbec poprvé vypočítali dynamiku (trajektorii) ukládání amyloidu u pacientů s DLB. Ukázali jsme, že dynamika ukládání amyloidu u DLB je velmi podobná té u AD demence. Na základě našich studií se domníváme, že někteří DLB pacienti by mohli v budoucnu profitovat z biologické anti-amyloidové léčby. Pomocí multimodalitního zobrazení jsme přispěli k pochopení patofyziologických procesů vývoje DLB a významné role amyloidové a tau ko-patologie, která ovlivňuje DLB fenotyp, prognózu a přežití pacientů s DLB.

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10. Overview of author's publications

Dr. Nedelska's cumulative impact factor is around 287.5, H-index is 21 and 1094 citations (WOS)

10.1. Original research which is basis of the dissertation: papers with IF

1. **Nedelska Z**, Andel R, Laczó J, Vlcek K, Horinek D, Lisy J, Sheardova K, Bures J, Hort J. Spatial navigation impairment is proportional to right hippocampal volume. *Proc Natl Acad Sci U S A.* 2012 Feb 14;109(7):2590-4. ***IF 9.737***
2. Laczó J, Andel R, **Nedelska Z**, Vyhnalek M, Vlcek K, Crutch S, Harrison J, Hort J. Exploring the contribution of spatial navigation to cognitive functioning in older adults. *Neurobiol Ageing.* 2017 Mar;51:67-70. ***IF 4.454***
3. Amlerova J, Laczó J, **Nedelska Z**, Laczó M, Vyhnálek M, Zhang B, Sheardova K, Angelucci F, Andel R, Hort J. Emotional prosody recognition is impaired in Alzheimer's disease. *Alzheimers Res Ther*. 2022 Apr 5;14(1):50. ***IF 8.823***
4. **Nedelska Z**, Przybelski SA, Lesnick TG, Schwarz CG, Lowe VJ, Machulda MM, Kremers WK, Mielke MM, Roberts RO, Boeve BF, Knopman DS, Petersen RC, Jack CR Jr, Kantarci K. ^{1}H-MRS metabolites and rate of β-amyloid accumulation on serial PET in clinically normal adults. *Neurology.* 2017 Sep 26;89(13):1391-1399. ***IF 8.689***
5. **Nedelska Z**, Ferman TJ, Boeve BF, Przybelski SA, Lesnick TG, Murray ME, Gunter JL, Senjem ML, Vemuri P, Smith GE, Geda YE, Graff-Radford J, Knopman DS, Petersen RC, Parisi JE, Dickson DW, Jack CR Jr, Kantarci K. Pattern of brain atrophy rates in autopsy-confirmed dementia with Lewy bodies. *Neurobiol Ageing.* 2015 Jan;36(1):452-61. ***IF 5.113***
6. **Nedelska Z**, Schwarz CG, Boeve BF, Lowe VJ, Reid RI, Przybelski SA, Lesnick TG, Gunter JL, Senjem ML, Ferman TJ, Smith GE, Geda YE, Knopman DS, Petersen RC, Jack CR Jr, Kantarci K. White matter integrity in dementia with Lewy bodies: a voxel-based analysis of diffusion tensor imaging.*Neurobiol Ageing.* 2015 Jun;36(6):2010-7. ***IF 5.113***
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11. Appendix: published thesis manuscripts in extenso