CHARLES UNIVERSITY
Second Faculty of Medicine

Summary of the Dissertation

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

Zuzana Nedelská

Prague, 2023

The Dissertation was written during part-time doctoral study programme Neurosciences at the Department of Neurology, Second Faculty of Medicine, Charles University.

Opponents:

The defence will take place before the Board for the Defence of the Subject Area Board
on…………………………in…………………………………… From
.... hours

....
Chairman of the Board for the Defence of Dissertations in doctoral study programme Neurosciences

Prof. MUDr. Jan Laczó, Ph.D., Department of Neurology, Charles University, Second Faculty of Medicine and Motol University Hospital
The Chairman of Subject Area Board and guarantor of the doctoral study programme Neurosciences

The Dean of the Faculty: prof. MUDr. Marek Babjuk, CSc.

The dissertation is available for inspection at the Department for Ph.D. Study of the Dean´s Office, Second Faculty of Medicine, Charles University, V Úvalu 84, 150 06 Praha 5 (phone 224 435 836).

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

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 amyloid a tau 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

Content

1. Background

1.1. Alzheimer's disease (AD) and AD diagnosis

AD is the most common cause of the dementia syndrome, accounting for 55-70 % dementia cases. 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+ is living with dementia, and the females are twice as much affected as males (report of the Czech Alzheimer Society 2020).

Pathologically, AD is characterized by extracellular accumulation of diffuse Aß and more deleterious dense, fibrillar (neuritic) plaques (Thal et al., 2002) and intracellular accumulation of neurofibrillary tau tangles (NFTs, Braak and Braak, 1995). On macroscopic level, the progressive abnormal accumulation of these proteins translates to the progressive neuronal loss perceived as an atrophy on visual inspection, and functionally translates to cognitive impairment. Currently, the most widely accepted hypothesis is that amyloid accumulation subsequently triggers abnormal tau accumulation. Biochemical and pathophysiological changes consistent with AD begin years to decades before the clinical symptoms are apparent (Villemagne, 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 on neuropsychological tests and brain atrophy on MRI especially in medial temporal (MTL) regions, which recapitulates the progression of AD-related neuropathology.

AD exists in a continuum of clinico-pathological changes, with the earliest stage, the preclinical stage without any objective cognitive impairment is being followed by stage of mild cognitive impairment (MCI) and then the full-blown dementia stage.

Based on the knowledge of pathophysiological changes, and the resulting cognitive changes, the National Institute of Aging and the Alzheimer's Association wrote diagnostic recommendation for the preclinical stage (Sperling et al., 2011), for MCI (Albert et al., 2011) and AD dementia (McKhann et al., 2011).

- Preclinical stage is consistent with intact cognitive functioning and an evidence of AD-related pathophysiology which is based on the assessment of designated biomarkers

- MCI stage demonstrates the evidence of cognitive decline from the previous cognitive level of a given individual who performs 1-1.5 standard deviation below age and education-matched norms in one or more cognitive domains but remain independent in everyday functioning

  o Amnestic MCI (aMCI) is characterized by memory deficit

  o Nonamnestic MCI (naMCI) is predominantly characterized by non- memory cognitive deficit.

- Dementia stage is characterized by the loss of independence in everyday functions, and there is an evidence of cognitive decline in at least two cognitive domains

However, these stages can be associated with any underlying aetiologies including various neurodegenerative disorders other than AD and a multitude of non-neurodegeneretaive aetiologies such as vascular disease, and others.

Thus, AD diagnosis should be supported by evidence of AD-related biomarkers when possible for research purposes.

For this reason, 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. In A/T/N the acronyms denote:

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

1.2. Conventional and advanced MRI methods in aging and dementia

In recent decades, structural imaging has transitioned from being used to exclude other, potentially treatable conditions like tumor, stroke, or normal pressure hydrocephalus to being used to diagnose specific neurodegeneration along with other diagnostic modalities, monitor disease progression, or being used as a surrogate measure of outcome in clinical trials.

1.2.1. Structural MRI

Brain atrophy is a visualization of neurodegeneration. Atrophy from T1-weighted MRI volumetry correlates with autopsy neuronal counts (Bobinski et al., 1999). MRIs of typical AD show hippocampal and MTL atrophy (Jack et al., 2002). In cross-sectional and longitudinal studies, MRI atrophy correlates with cognitive impairment (Jack et al., 2002). MRI atrophy matches Braak staging, from early entorhinal cortical and basal forebrain atrophy to whole brain atrophy in AD as disease progresses. MTL atrophy in MCI patients predicts AD dementia, but alone it has 50–70% specificity and sensitivity (DeCarli et al., 2007). Regional atrophy is clinically associated with a specific cognitive impairment, such as lower Auditory verbal learning memory test performance correlates with hippocampal atrophy, although it is not aetiology-specific. Despite this, MTL atrophy is regularly utilized in differential diagnosis in clinics and research.

1.2.2. Diffusion tensor imaging (DTI)

DTI requires more technical knowledge and computation, but for a change, it offers a unique perspective on anatomy of microstructure of gray and especialy white matter (WM). DTI uses the anisotropic diffusion of water molecules perpendicular to WM fibres. Water diffusion changes when myelin sheaths, cell membranes, or intracellular components are disrupted. Fractional anisotropy (FA), decreases proportionally with WM degradation (Pierpaoli & Basser, 1996). FA may be used as a surrogate for WM integrity (Carmichael & Lockhart, 2012). Mean diffusivity (MD), inversely proportional to FA, measures all-directional water movement, and is better than FA at studying cortical microstructure. These two DTI metrics show changes in early presymptomatic AD and in progression of MCI to AD dementia (Nir et al., 2013). Higher MD and lower FA in AD-typical regions correlates with NFT Braak stageing and clinical disease severity in AD patients (Kantarci al., 2017).

1.2.3. Arterial spin labeling (ASL)

ASL in an advanced MRI technique that uses blood water molecules as endogenous magnetically tagged tracers to assess regional cerebral blood flow of a brain tissue (Detre et al., 2009; Williams et al., 1992). Since brain glucose metabolism and blood perfusion are interconnected, ASL provides a possible alternative to FDG PET (Madsen et al., 1995). ASL is more affordable, accessible and less invasive than FDG PET. Despite advantages of ASL, the technological implementation and image processing requirements have prevented its widespread adoption so far.

1.2.4. Proton magnetic resonance spectrocopy (^{1}H-MRS)

1H-MRS resonance spectroscopy can quantify multiple brain tissue metabolites in a single MRI scan using one or more brain voxels. Single-voxel H-MRS is usually taken from the posterior cingulate cortex, a region associated with early AD

changes. While creatine levels have been steady in diverse pathological processes and utilized as internal reference in H-MRS, other metabolites have been associated with various

cellular and molecular pathophysiological processes. N-acetyl-aspartate (NAA) is mostly found in neuronal bodies and axons and is used to measure neuronal density and survival. AD patients with NFT tau pathology have lower NAA brain levels. Glia produce myo-inositol (mI), which increases with glial proliferation and neuroinflammation (Glanville et al., 1989). AD patients have lower NAA and higher mI levels than cognitively normal peers (Huang et al., 2001). Increasing mI levels were associated with lower CSF Aß42 levels, higher Aß accumulation on PET, and higher Aß load at autopsy in clinically unimpaired older persons who may be at risk of developing AD (Voevodskaya et al., 2016).

1.3. Experimental cognitive evaluation in AD: spatial navigation (SN)

Traditional neuropsychology tests, altghough a golden standard in cognitive function evaluation are language- and culture-dependent. AD affects sensory, emotional, and social cognition beyond paper-and-pencil based traditional tests.

SN allows organisms and people to move purposefully towards their goal. Accurate SN requires complicated processing of visual, auditory, somatosensory, vestibular, and prorioceptive input (Bates & Wolbers, 2014), and involves a whole brain network (Chen, et al., 2021). SN performance deteriorates throughout normal aging (Cerman et al., 2018), but it is significantly impaired in early AD (Hort et al., 2007; Laczo et al., 2012b). Two basic SN strategies are: 1. Egocentric or body-centered SN that uses the individual's body position and bodily axes for navigation. The posterior parietal cortex, precuneus, and nucleus caudatus are most involved in this strategy (deIpolyi et al., 2007; Weniger et al., 2011). 2. Allocentric or world-centered SN that uses external landmarks for navigation, creating a mental representation of the area, landmarks, and destination. This strategy is independent of one's position, and is associated with the hippocampus (Maguire et al., 1998),

the enorhinal and parahippocampal cortex (Ekstrom et al., 2003), as well as structures outside the MTL like the basal forebrain, and prefrontal cortices (Moffat et al., 2007). The human analogue of the Morris water maze (hMWM) called the Hidden Goal Task has beenvalidated and used to measure spatial navigation at different stages of AD (Laczo et al., 2012a; Laczo et al., 2012b).

1.3.1. 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). Neuropsychiatric symptoms are also a major predictor of institutionalization (Schoenmakers et al., 2009). Research findings suggest that neuropsychiatric symptoms may stem from social cognition deficits. It includes facial expression recognition, empathy, and moral processes including prosocial behavior. Neuropsychiatric disorders are especially associated with an impaired perception of emotions (Santamaria-Garcia et al., 2020).

Emotional recognition involves perception, social judgment, interoception, and expressiveness (Adolphs et al., 2002). Communicating through gestures, facial expressions, voice, and prosody—the acoustic qualities of speech as rhythm, melody, tone, and volume—requires precise emotional processing and recognition. Social connections, relationships, and everyday interactions suffer from impaired emotional perception. MCI and AD dementia patients had poor emotional recognition (Elferink et al., 2015). Emotional recognition has been linked to temporal structures, especially right-sided ones like the amygdala, anterior cingulate cortex, and temporal pole (Gallagher & Chiba, 1996), which are also linked to AD. More research is needed to improve social cognition in AD and other neurodegenerations.

1.4. Dementia with Lewy bodies (DLB)

DLB is a clinical syndrome characterized by a presence of cognitive impairment (dementia) and (at least some) core features of: spontaneous parkinsonism, (recurrent) visual hallucinations, REM sleep behavior disorder (RBD), 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. The prevalence studies have reported a wide range of proportions of DLB patients, with a mean prevalence of 7.5 % in clinic-based studies. These are likely underestimated 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.

DLB is pathologically defined by underlying Lewy body disease (LBD). Together with 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 which leads to neurodegeneration. However, AD-related pathology, Aβ plaques and NFT-tau, do frequently overlap with LBD (Schneider et al., 2007).

Overlapping AD pathology can obscure typical DLB-related clinical features and makes premortem diagnosis challenging. This applies especially to DLB patients with high degrees of AD co-pathology, who are often clinically diagnosed as having AD (Merdes et al., 2003). Mixed DLB/AD patients clinically progress faster, cognitively decline faster (Rongve et al., 2016), are independent shorter and survive

shorter (Lemstra et al., 2017) than DLB without AD co-pathology.

1.4.1. DLB diagnosis

The 2017 report of the fourth DLB Consortium (McKeith et al., 2017) 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. 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 1 below graphically summarizes the core and supportive clinical features and indicative and Supportive biomarkers used to make a diagnosis.

	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			
	yes	1 feature		≥ 1 biomarker	
Possible DLB	yes	1 feature			
	yes	0		≥ 1 biomarker	

Supportive DLB clinical features 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.

1.4.2. DLB biomarkers

Unlike the AD field, there are no direct in vivo biomarkers of LB disease or α-synucleinopathy, although there are multiple indirect biomarkers.

1.4.2.1. DaT scan: suggestive biomarker

DaT radionuclide (^{123}I-ioflupane) PET or SPECT demonstrates reduced postsynaptic dopamine transporter uptake in basal ganglia. DaT scan can identify DLB from AD (specificity 90%, sensitivity 78%) (McKeith et al., 2007). Thus, if a patient has dementia, one core DLB symptom, and an abnormal DaT scan, we can make a diagnosis of probable DLB. However, DaT scan alone cannot reliably distinguish DLB from PD/PDD or other atypical parkinsonisms and some DLB patients without parkinsonism may have normal DaT scans or unusual but not entirely abnormal DaT scans.

1.4.2.2. MIBG scan: indicative biomarker

[123]I-metaiodbenzylguanidine myocardial SPECT demonstrates diminished postganglionic sympathetic innervation in the heart muscle scaled by mediastinum (heart-to-mediastinum ratio) and indicates early LB. RBD patients and MCI patients with LB core features commonly have lower ratio on MIBG scans. In milder DLB cases, the specificity was suggested to be 94% (Yoshita et al., 2015). MIBG scans can also assist in differentiating parkinson plus syndromes. However, various medicines, ischemic heart disease, peripheral neuropathies, heart failure, diabetes, and others might bias MIBG scans.

1.4.2.3. Polysomnography (PSG): indicative biomarker

PSG is used to confirm the RBD without atonia. RBD without atonia is highly

specific predictor of LB pathophysiology (Boeve et al., 2013). A patient with dementia and a positive history of RBD, followed by a PSG that confirms RBD without atonia, can have a diagnosis of probable DLB assigned.

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

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) and also rates of atrophy in hippocampus and amygdala on longitudinal measurements (Nedelska, et al., 2015; Whitwell et al., 2007). Thus, observing minimal MTL atrophy on MRI is typical for (pure) DLB but would not be so 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, and suggests an overlapping pathology (most likely AD) and more aggressive disease, and faster disease progression.

1.4.2.5. Reduced occipital glucose metabolism and cingulate island sign on FDG- PET: 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 (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.

Recent research and clinical research efforts have been focused on prodromal DLB (MCI with LB core features or biomarkers) to aid timely diagnosis and intervention.

2. Objectives

The overarching purpose of this dissertation thesis has been to contribute to the timely diagnosis of Alzheimer's disease and dementia with Lewy bodies, incorporating experimental neuropsychology tests and multimodality imaging methods. The potential general application 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 with my foreign fellowships, **the main aims are organized into three major groups**, and corroborated into specific aims:

- first aim is associated with studies using 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 aim is associated with studies on multimodality imaging in DLB to better understand the complex biology of DLB.

2.1. 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: Spatial navigation impairment is proportional to right hippocampal volume

The aim of the study was to (1) 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; (2) 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 hypothesized that: (1) allocentric spatial navigation accuracy would be proportional to the right hippocampal volume (atrophy) irrespective of the whole brain atrophy; (2) association between allocentric spatial navigation performance and the right hippocampal volume (atrophy) would be stronger in elderly with a cognitive impairment versus intact peers; (3) findings from the real-space 3-dimensional setting would correlate with computerized 2-dimensional test, with practical implications of this finding.

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

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

We hypothesized that: (1) performance on paper-and-pencil based neuropsychological tests in the six established domains would be separated from performance in allo- and egocentric spatial navigation task; (2) however, the performance in the established cognitive domains would still be associated with allocentric and egocentric spatial navigation; (3) right hippocampal volume, a structure impaired early on in AD and 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: Impaired recognition of emotional prosody in AD

The aim of study III was to (1) examine emotional prosody recognition (EPR) in participants with aMCI due to AD, AD dementia patients, and cognitively unimpaired controls; and to (2) assess the associations of EPR performance with

measures of the relevant regional brain volumes or cortical thickness; (3) explore whether the EPR score is associated with a cognitive impairment by MMSE and whether EPR score can be used to distinguish among the diagnostic groups.

We 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, sulcus temporalis superior, 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.

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

The aim of study IV was to utilize a single time-point 1H-MRS for predicting longitudinal accumulation of Aß on 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: Pattern of brain atrophy rates in autopsy-confirmed DLB

The aim of study V was to (1) investigate the pattern and the magnitude of longitudinal rates of atrophy in autopsy-confirmed DLB patients and to (2) 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) the sample size estimations for a hypothetical clinical trial recruiting patients with DLB and mixed DLB/AD pathologies would benefit from the atrophy rates used as surrogate outcome measures.

2.4.2. Study VI: White matter integrity in DLB: a voxel-based analysis of diffusion tensor imaging

The aim was to (1) determine white matter impairment in DLB patients using DTI technique and to (2) determine the effect of Aß load by PET on the white matter integrity in DLB.

We hypothesized that (1) the disruption of white matter in DLB patients would be of different distribution and smaller magnitude than in AD patients; (2) AD-related pathology represented by amyloid load from PET may contribute to the white matter disruption in DLB patients.

2.4.3. Study VII: Regional cortical perfusion on arterial spin labelling MRI in DLB: Associations with clinical severity, glucose metabolism and tau PET

The aim of this study was (1) to assess the patterns of cortical hypoperfusion using a non-invasive arterial spin labelling MRI in DLB as compared to more invasive and expensive glucose FDG PET, and (2) to assess the effect of AD-related pathology

by tau PET on the pattern of cortical hypoperfusion in DLB.

We hypothesized that: (1) a voxel-wise pattern of perfusion MRI would be similar to glucose metabolism on PET; (2) the CIS ratio would be similar between the two imaging techniques, supporting the interchangeability of both imaging methods; and (2) overlapping AD tau-related pathology by tau PET would decrease the CIS ratio and cause the 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: Association of longitudinal ß-amyloid accumulation determined by PET with clinical and cognitive decline in probable DLB

The aim of study VIII was to (1) determine the trajectory of longitudinal Aß accumulation in DLB patients and to (2) determine associations of longitudinal Aß accumulation with clinical and cognitive decline over time.

We hypothesized that: (1) the trajectory of longitudinal Aß accumulation in DLB patients would not be linear, based on the known trajectories of Aß accumulation 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: Longitudinal atrophy in prodromal DLB points to cholinergic degeneration

The aim of this study was to (1) investigate the pattern and magnitude of both, regional cross-sectional and regional longitudinal rates of atrophy in patients with prodromal DLB (MCI-LB) and (2) associations of atrophy rates with clinical disease progression.

We hypothesized that (1) 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 (2) the longitudinal rates of atrophy would reveal more wide-spread patterns of atrophy compared to snapshot-like cross-sectional measurements in prodromal DLB; and (3) regional rates of atrophy would correlate with longitudinal measures of clinical and cognitive decline in prodromal DLB.

2.4.6. Study X: Cerebrovascular disease, neurodegeneration, and clinical phenotype in DLB

The aim of this study was to (1) assess different aspects of cerebrovascular disease (CVD) in a multinational cohort of DLB patients and to (2) ascertain the contribution of cerebrovascular disease to clinical phenotype in DLB using a multi-site international cohort. **We hypothesized** that (1) DLB patients would show relatively significant CVD in their brains, and that (2) the overlapping CVD would obscure the clinical phenotype in DLB patients.

3. Materials and methodology

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 Brain Aging Study (CBAS) cohort** at the Cognitive center, Department of Neurology, Motol University Hospital and the Second Faculty of Medicine, Charles University in Prague, in part collaborating 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.

3.1.1. CBAS cohort

CBAS is a prospective, observational, longitudinal, multi-centric cohort study on aging and dementia in Central Europe including those who are 55 years old or more. The main goal of CBAS is to investigate risk or potentially protective factors associated with cognitive decline and dementia including well-established and novel biomarkers. CBAS predominantly focuses on early stages of AD such as SCD and MCI. However, many patients with dementia such as AD, FTLD and DLB are recruited to CBAS+ cohort. All participants are extensively evaluated using traditional and experimental neuropsychology of all cognitive domains, brain MRI, by neurologic examinations and semi structured interviews on history and medication, lab test, measurements of physiological functions, by various questionnaires targeted at life-style and behaviour, and by blood-based biomarkers. Subset has CSF sampled and/or brain amyloid PET performed. The detailed information on the study has been published in Cohort profile in BMJ Open by Sheardova et al., 2019. The website of CBAS can be accessed at website is www.cbas.cz. For comparison, cognitively unimpaired older volunteers as 'controls' are recruited from the University of the third age at our faculty or from patients' significant others of similar age.

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 prospective, longitudinal, observational cohort studies. MCSA is a population-based cohort focused on aging, located in the Olmsted County in Minnesota, USA, and ADRC is clinic-based study on dementia. The evaluations are comprehensive and multimodality, and a special emphasis is put on imaging methods including multimodality longitudinal PET (tau, FDG and amyloid). Both studies are well-established and known internationally. The methods have been published extensively (Roberts et al., 2012).

3.1.3. European Dementia with Lewy Bodies consortium

Our study collaborates with European Dementia with Lewy bodies consortium (E-DLB), a multi-center and global scientific initiative with a main objective to establish international consensus diagnostic criteria for DLB and for prodromal DLB, and to create representative and high-quality biomarker data and 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 with E-DLB. Website of the E-DLB can be accessed at www.e-dlb.com

3.2. Experimental neuropsychology in CBAS relevant to this dissertation

3.2.1. The spatial navigation testing by the Hidden Goal Task (HGT)

HGT used in Study I and Study II is performed in a 2-dimensional virtual environment on the computer screen and in a 3-dimensional real-space environment, a human analogue to Morris Water Maze. Test is designed to examine egocentric (self-centered, using our body position towards the goal) and allocentric (world- centered, using external landmarks and their relationship towards the goal) spatial navigation strategies. Allocentric delayed spatial

navigation is also examined. Participants are orientating and finding the most accurate position of the hidden goal. The difference between the correct position of the goal and position guessed by participants determines the distance error in cm (real-space) or pixels (computer screen). Each subtask targeted at specific navigational strategy has eight trials, and the distance errors are averaged. The delayed task has two trials. HGT methods have been repeatedly published by CBAS authors (Hort et al., 2007; Laczo et al., 2012a; Laczo et al., 2014).
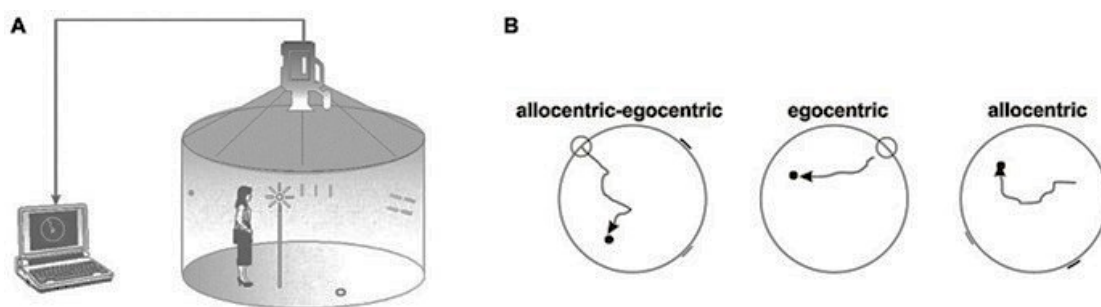
Figure 1. demonstrates A. the real-space 3-dimensional setting of the HGT, an enclosed arena with 2.8m diameter and 2.9m tall with a goal projected to the floor and navigational cues to its diameter; and B. the schematic of the 2-dimensional computerized version with specific subtasks associated to specific strategies of spatial navigation. Courtesy of Dr. Kamil Vlcek, adapted from Gazova et al., 2013. The mixed allocentric-agocentric is the easiest task, hence the test starts with this one, each patient having eight attempts to locate a hidden goal.

3.2.2. The prosody test of emotion recognition from vocal recording

In study III under Aim 1 we used the Emotional Prosody Recognition (EPR) rest developed at our site in collaboration with professional actors who prepared 3 second long recordings of sentences with neutral semantic meaning using a distinct emotional tone of voice representing five emotions of rage, disgust, sorrow, fear and joy. Cognitively normal volunteers from our hospital, unrelated to the study, selected 25 most representative recordings, each emotion five times, for the test battery administered by trained personnel to patients by playing the sentences on a computer using headphones. Patients were required to choose the most accurate emotion after each recording using a list of five given emotions (Amlerova   et   al.,   2022).

3.3. Brain imaging

3.3.1. CBAS imaging relevant to this thesis

Participants from studies I-III and study X have been scanned at 1.5T Siemens Avanto scanner at baseline and annual or biannual follow-ups. Scans are obtained to exclude other pathologies potentially interfering with cogniton (such as tumours, hydrocephalus, stroke. etc) and to obtain anatomical information to judge global and regional brain atrophy either visually using visual semi quantitative scales or for quantitative volumetry using 3-dimensional volumetric MPRAGE sequence. This sequence is used to derive the estimated total intracranial volume to correct for the differences in head size, the whole brain and ventricular volumes, volumes of subcortical structures including the hippocampus and amygdala, and regional cortical thickness, areas and volumes such as entorhinal, cingulate, parietal, parahippocampal cortical thickness and others. Volumetry is performed a trained personnel using an automated, well-established algorithm FreeSurfer, detailed at:

https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki.

Other sequences are used to ascertain small vessel disease using visual rating scales or quantitavely using FLAIR sequence, DTI for white matter microstructure or T2* sequence to count microbleeds. Our imaging protocol is harmonized with similar international studies on aging such as ADNI.

3.3.2. Imaging at Mayo ADRC and MCSA

The imaging study here has been established by Dr. Clifford R. Jack, Jr., a radiologist who initially described a hippocampal atrophy as hallmark of AD and operatinalized hippocampal atrophy measurements. He later proposed the model of temporal evolution of AD biomarkers and A/T/N classification. The PI of Mayo Clinic aging studies, Dr. Ronald C. Petersen, coined the term of mild cognitive impairment. Mayo Clinic is also a central coordinating site of ADNI imaging methods, and contributes to many white papers on utilization of multimodality

imaging for clinical and clinical research purposes. All major MRI and PET methods are performed here, and a large core of medical programmers, physicists and data analysts are developing either entirely new or optimizing available image analysis algorithms for image quantification. Each of studies IV-X has a specific image analysis approach described in detail in published manuscripts.

3.4. Approach to data analysis

The study designs in this dissertation are case-control studies, either cross-sectional or longitudinal, or prospective longitudinal cohort studies. In each study, the most optimal analytical approach has been discussed with statisticians. Specific statistical tests and models have been 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 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.

4. Results

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. Bullet points provide the main finding of the study.

4.1. Aim 1, Study I.

- We showed that the right hippocampus is essential for human allocentric (world-centred) spatial navigation in the real space, and that the right hippocampal atrophy is associated with allocentric spatial navigation impairment in patients from AD continuum.

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) HGT 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.
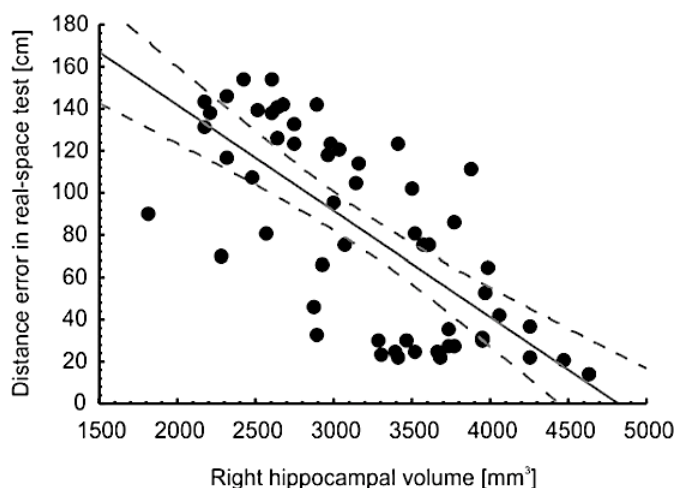

Figure 2. shows an inverse correlation between a smaller right hippocampal volume in mm3 and greater allocentric spatial navigation distance error cm in the real-space version of the HGT, r = -.0.71, p< 0.001 in the patient sample. Subsequent regression modelling adjusting for the most important variables confirmed this association (β = −0.62, P < 0.001, Nedelska et al.2012).
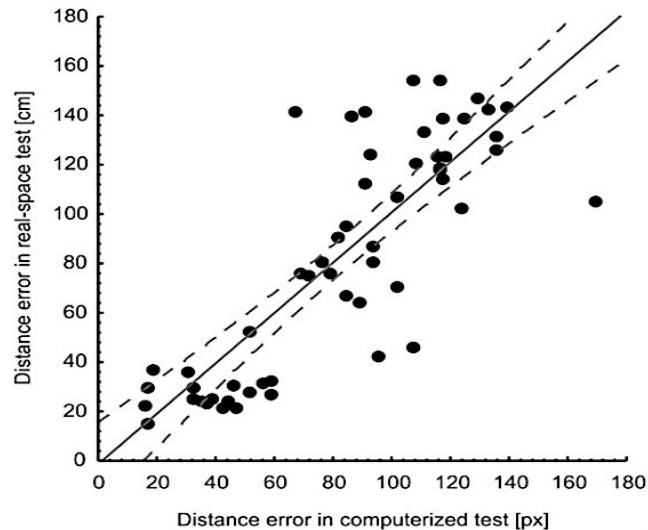
Figure 3. shows a positive correlation between findings from the computerized 2-dimensional version of the HGT and the real-space 3-dimensional version, r = 0.83, p < 0.001. This suggests that although the real-space and computerized version may not be entirely interchangeable, the PC version is a sufficient alternative, especially given its portability and user comfort of administration (from Nedelska et al., 2012).

4.1. 2. Aim 1, Study II.

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

In a factor analysis, allocentric and egocentric spatial navigation tasks from the real-space version of HGT 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.

4.1.3. Aim 1, Study III

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

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 could also discriminate controls versus aMCI, and aMCI versus dementia groups. EPR score was more reduced as illness severity increased, in correlation with MMSE.. Significant positive associations of EPR with right temporal pole, STS, and bilateral rostral anterior cingulate thickness were observed.
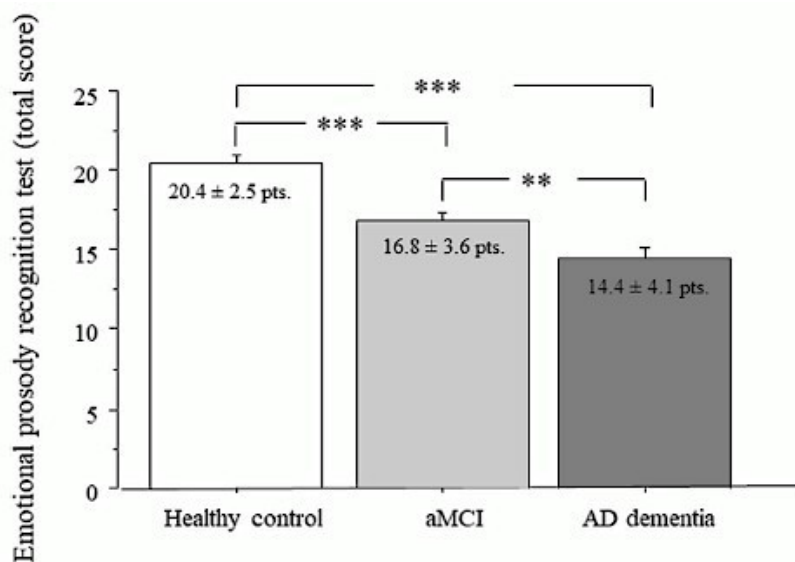

Figure 4. shows the histograms of the total emotional prosody recognition scores in prodromal AD (aMCI due to AD) and AD dementia compared to normal control group. **p<0.001, ***p< 0.0001 (Amlerova et al., 2022).

4.2. Aim 2, Study IV.

- 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.

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 1H-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.
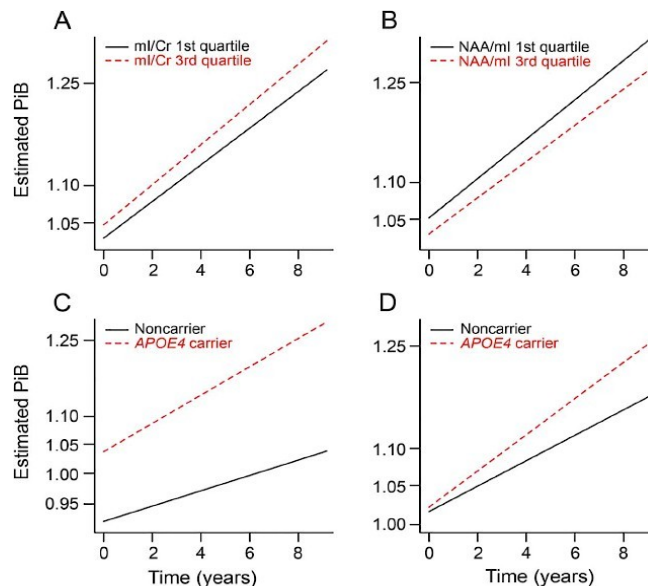

Figure 5. shows the estimates for the rate of ß-amyloid accumulation over time for a clinically normal older participant. Upper line shows the rate of ß-amyloid accumulation is predicted using an interaction between baseline H-MRS metabolite levels and time in a sense that: higher

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).
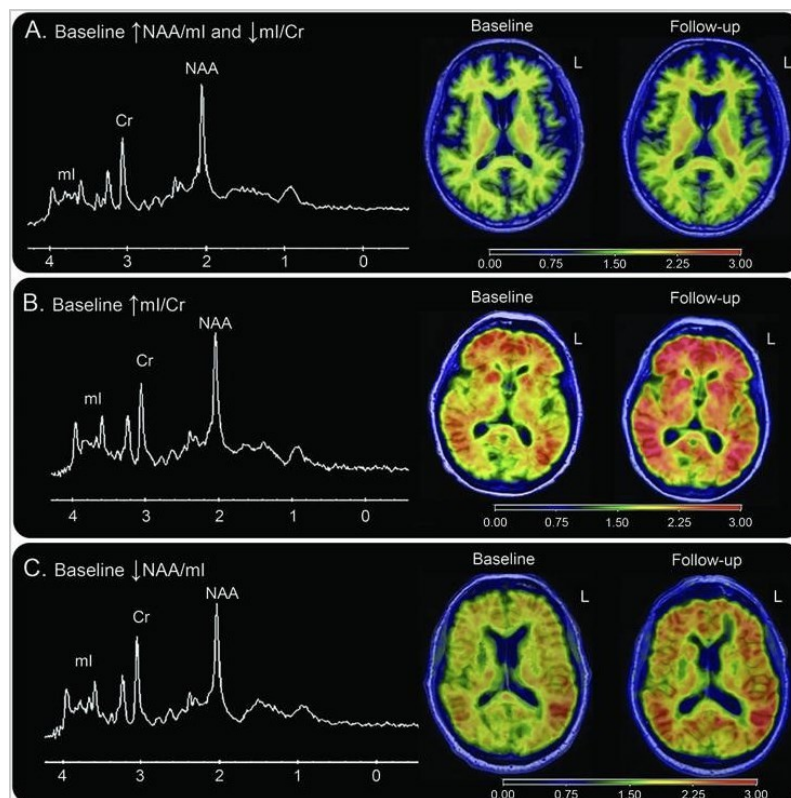

Figure 6. shows three cognitively normal participants, their baseline MRS metabolite levels, their matched baseline amyloid PET and follow-up PET findings. Person A has relatively high NAA/mI and low mI/Cr which can both work as markers of low amyloid load at baseline and low amyloid accumulation over 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).

4.3. Aim 3, Study V.

- 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.

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.
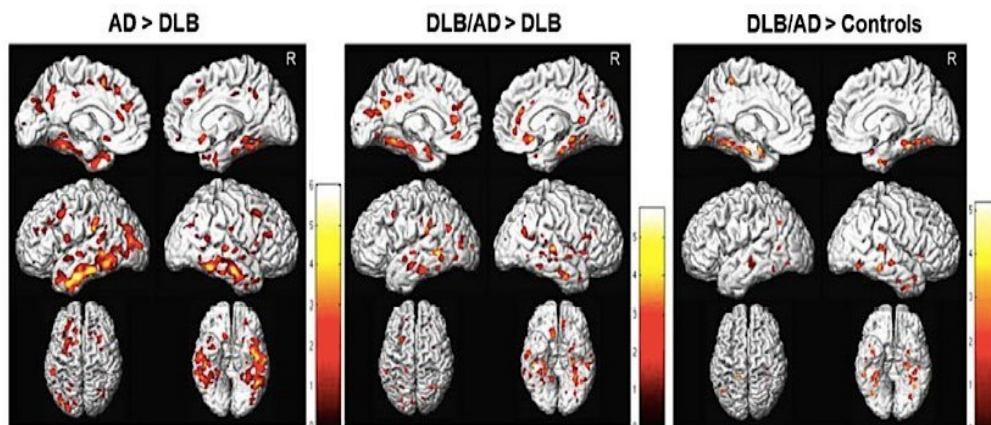

Figure 7. shows the voxel-wise pattern and the regional distribution of cortical rates of atrophy longitudinally between each two autopsy-confirmed groups. DLB vs controls are not shown because there were minimal differences in rates of atrophy (Nedelska, Ferman, et al., 2015).
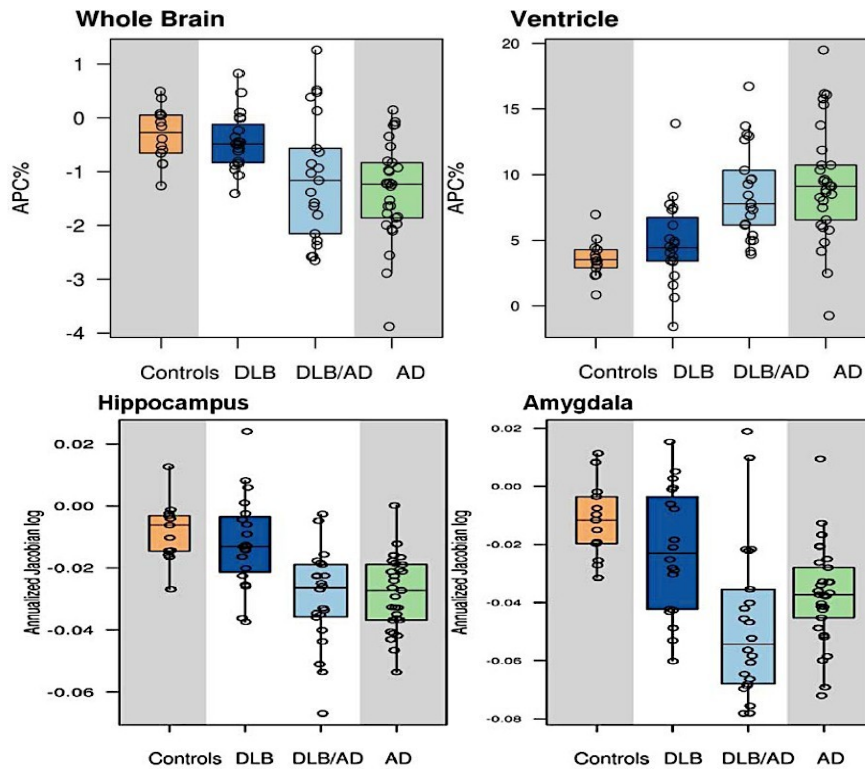
Figure 8. shows the atlas-based differences in global measures of atrophy such as whole brain or expansion of ventricles in the upper row. Lower row shows differences in rates of atrophy in medial temporal regions such as amygdala and hippocampus in the respective autopsy-confirmed groups (Nedelska, Ferman, et al., 2015).

4.3.1. Aim 3, Study VI

- 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.

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.
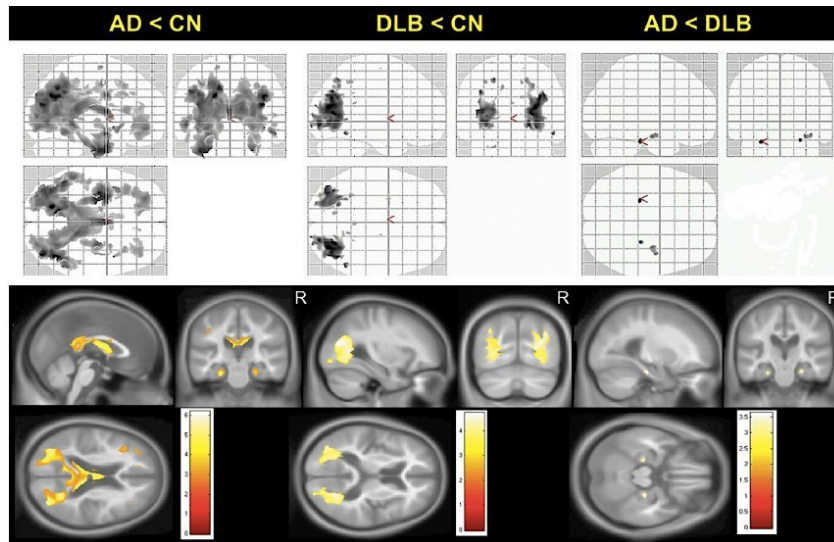

Figure 9. shows the voxel-wise differences between each two clinical groups in white matter integrity by fractional anisotropy derived from DTI. AD dementia patients show the most large-spread patter of white matter disruption, whereas it is more posteriorly distributed in DLB patients. AD patients still have more profound impairment in parahippocampal white matter (Nedelska, Schwarz, et al., 2015).
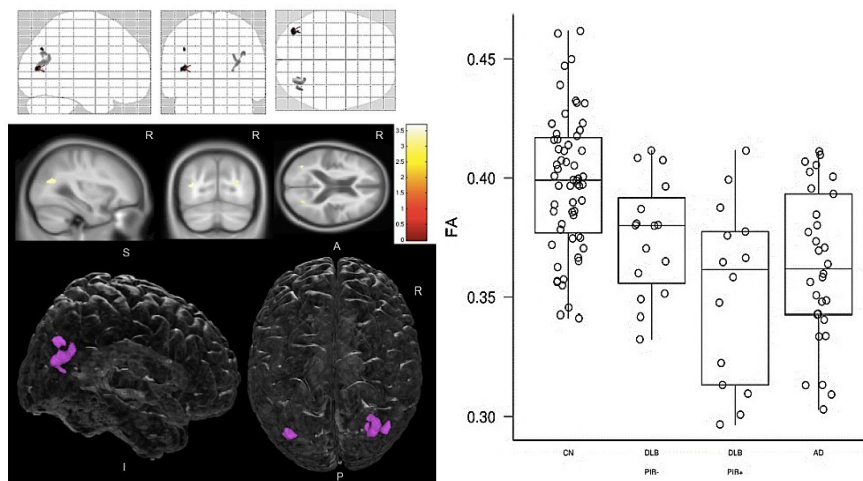
Figure 10. shows voxel-wise well circumscribed impairment of white matter strategically located at the cross-roads posterior temporal, parietal and occipital white matter in DLB compared to controls. This comparison is after adjusting for the effect of amyloid load from PET. Boxplots on the right show lower fractional anisotropy in this white matter parieto-occipital region when amyloid load is considered (Nedelska, et al., 2015).

4.3.2. Aim 3, Study VII

- 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.

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.
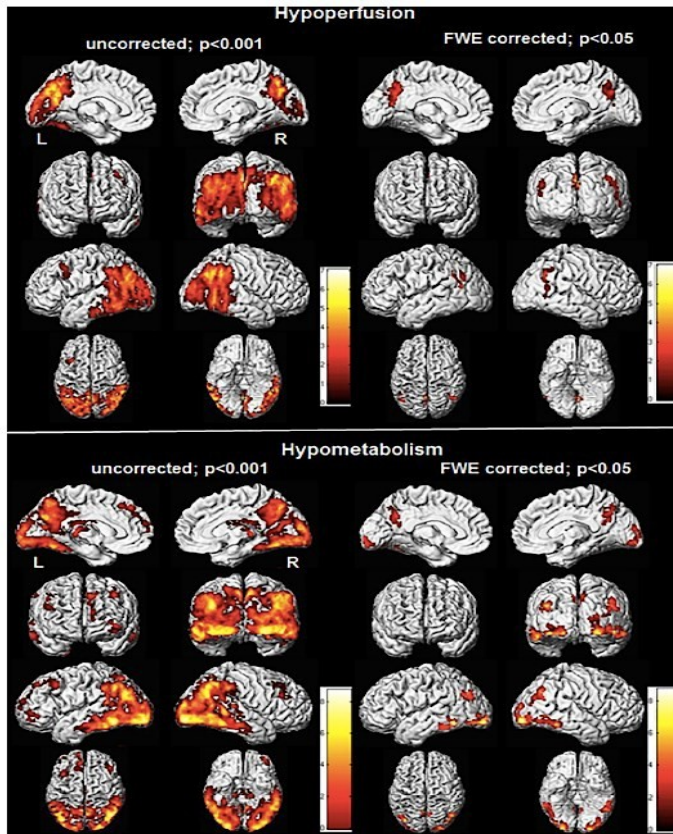
Figure 11. shows voxel-wise pattern – the distribution and the magnitude of hypoperfusion from ASL-MRI compared to pattern of glucose hypometabolism on FDG-PET in DLB patients (Nedelska et al., 2018). The similarities in patterns across these two methods are obvious, supporting the notion that perfusion and metabolism are two processes coupled together, thus the imaging methods potentially interchangeable for practical clinical purposes.
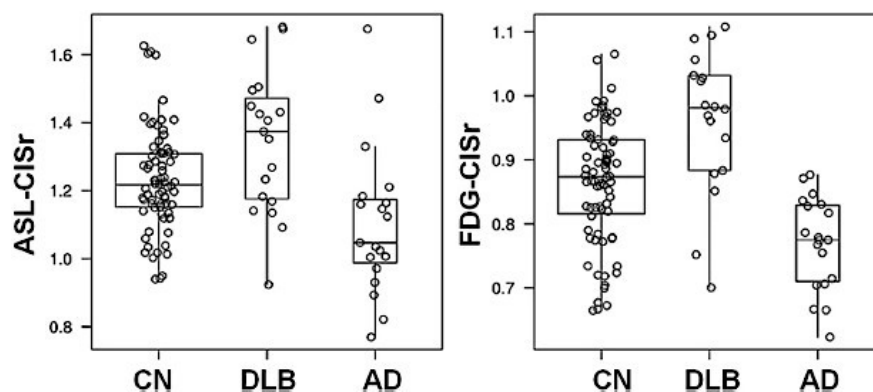

Figure 12. shows the very similar between-group differences in cingulate island sign ratio from ASL MRI (ASL-CISr) and glucose PET (FDG-CISr), the correlation between ratios is r = 0.67, p = 0.002 (Nedelska et al., 2018).
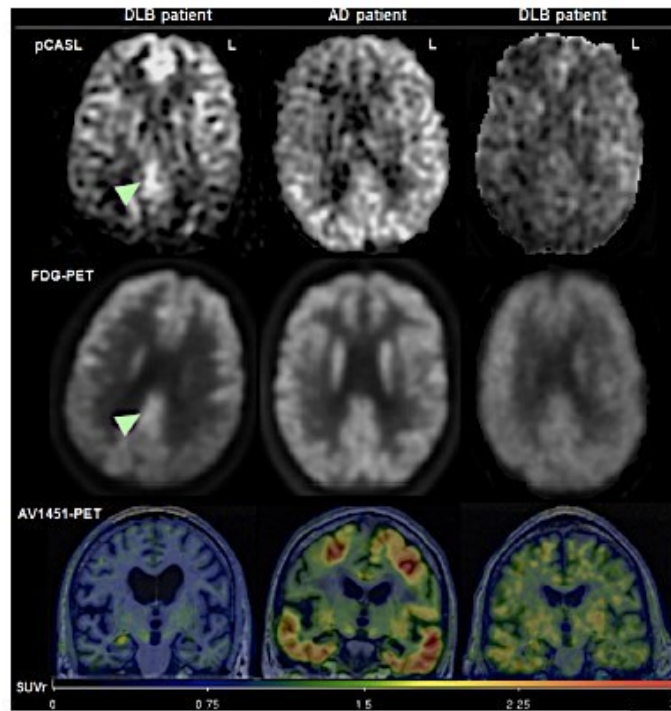
Figure 13. shows three individual patients and their respective findings on imaging methods. Left column is a typical DLB patient with visually preserved CIS (green arrowhead) both on perfusion ASL MRI (labelled as pCASL) and FDG-PET, who has low tau accumulation on AV 1451 tau PET. Middle column is 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).

4.3.3. Aim 3, Study VIII

- 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.

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; R^2 =0.215; change in PiB SUVR: regression coefficient [SE], 16.17 [7.47]; P=0.04; R^2=0.124) and the memory Auditory Verbal Learning Test, delayed recall (baseline PiB SUVR: regression coefficient [SE], -2.09 [0.95]; P=0.04; R^2=0.182; change in PiB SUVR: regression coefficient [SE], -25.05 [10.04]; P=0.02; R^2=0.221).

**Trajectory of longitudinal β-amyloid accumulation in DLB vs CU**
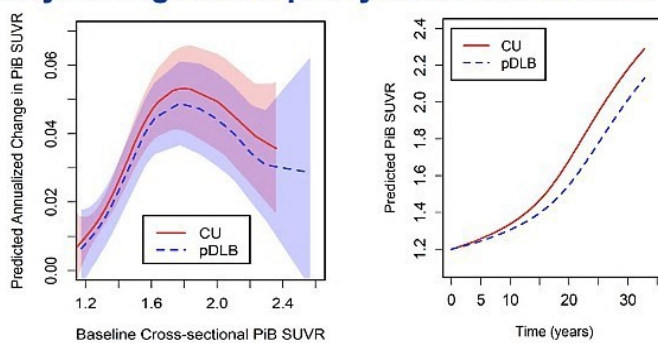
- Rates of Aβ accumulation accelerated, peaked around baseline PiB SUVR of 1.8 & then decelerated, forming an inverted U-shaped functional form
- Trajectories did not differ in DLB compared to CU in the shape (p=0.585) or in vertical shift (p=0.22)
- Integral relationship of amyloid (cumulative PiB SUVR) with time showed the sigmoid-shape functional form

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.
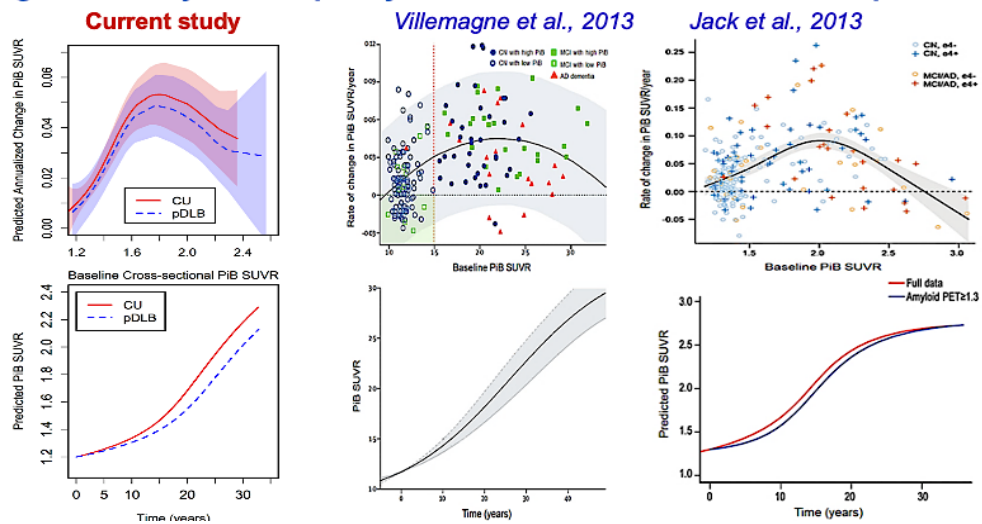
Panel 2. Emphasizes the current study findings in DLB (left column) when compared to other significant studies on longitudinal amyloid accumulation in AD continuum by Villemagne et al., 2013, middle column and Jack et al, 2013 right column. The similarity of amyloid accumulation curves in DLB and in AD (including prodromal and preclinical AD) is obvious.
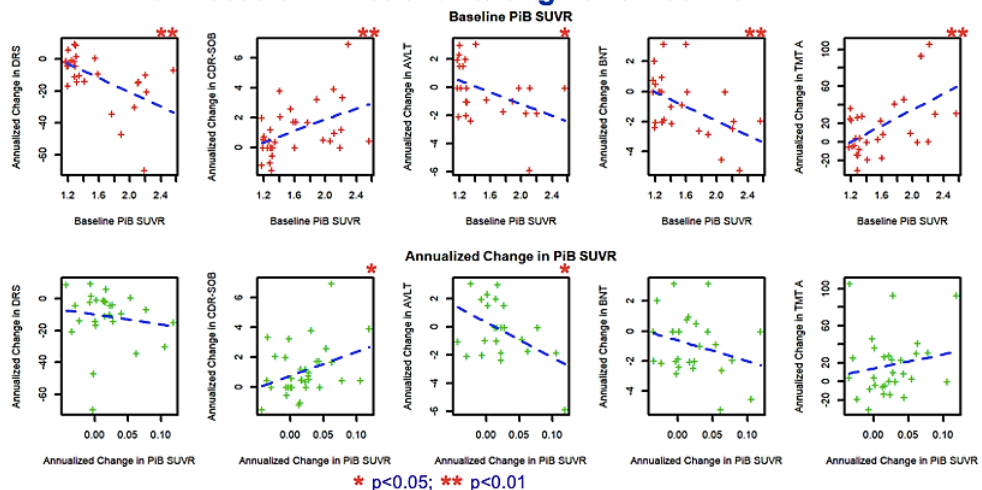
Panel 3. summarizes the associations among baseline cross-sectional amyloid accumulation (top row) and longitudinal amyloid accumulation (bottom row) as predictors and longitudinal change in functional and cognitive tests or scales as outcomes. Higher baseline amyloid predicts worsening in all depicted 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).

4.3.4. Aim 3, Study IX

- 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.

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.
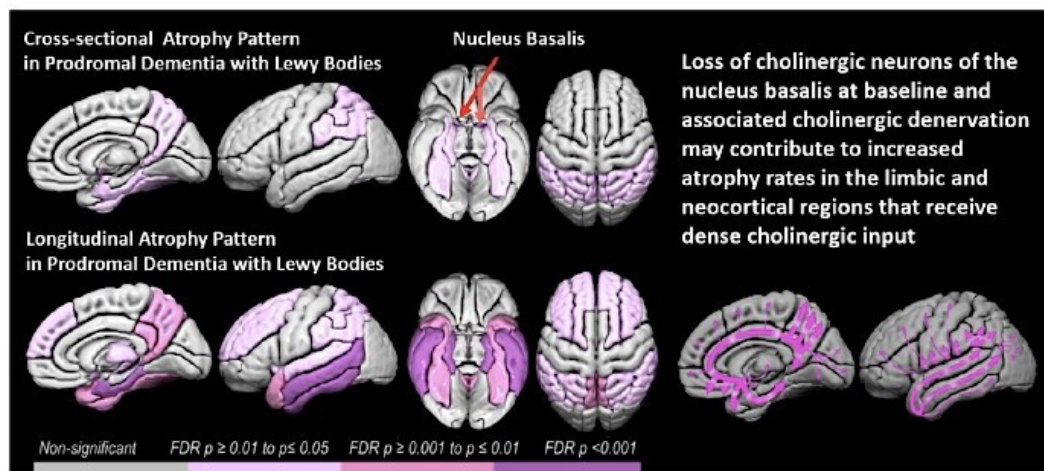
Panel 5. summarizes the main findings of the study, showing that prodromal DLB (MCI with core LB features) is characterized by relatively circumscribed atrophy at baseline (top row), especially in the cholinergic nucleus basalis of Meynert and temporoparietal cortices (pink shades). The longitudinal 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 of the cortical regions that receive dense cholinergic inputs from nucleus basalis of Meynert (Kantarci et al., 2022).
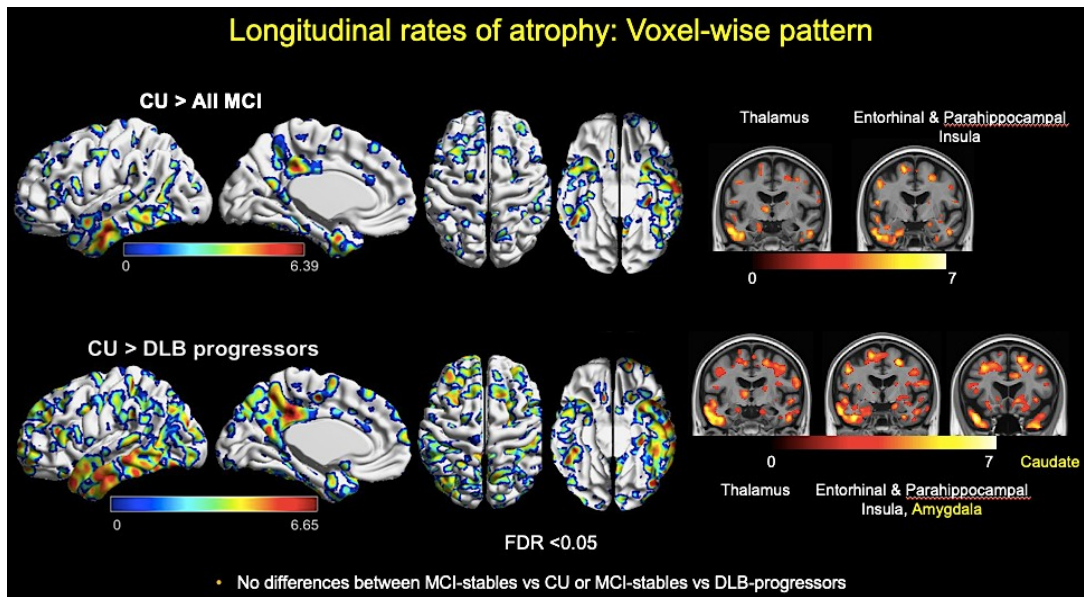
Figure 14. shows the pattern and the magnitude of the rates of atrophy over the time in prodromal DLB (all MCI-LB including those who remained stable over time and who progressed to full blown DLB, top row), and in those prodromal DLB who later progressed to full blown DLB (bottom row) compared to the 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.
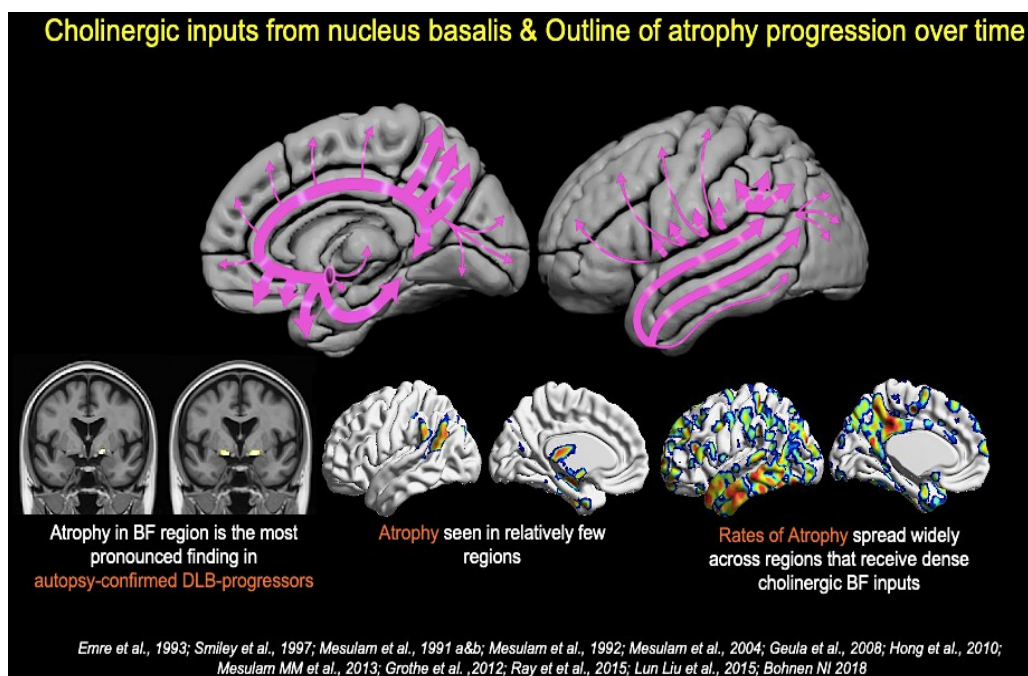
Figure 15. is a schematic representation of the cholinergic nucleus basalis of Maynert (pink circle in the basal forebrain area) and the cholinergic projections and their presumed strength into almost all cortical regions.

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).

4.3.5. Aim 3, Study X

- 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.

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.
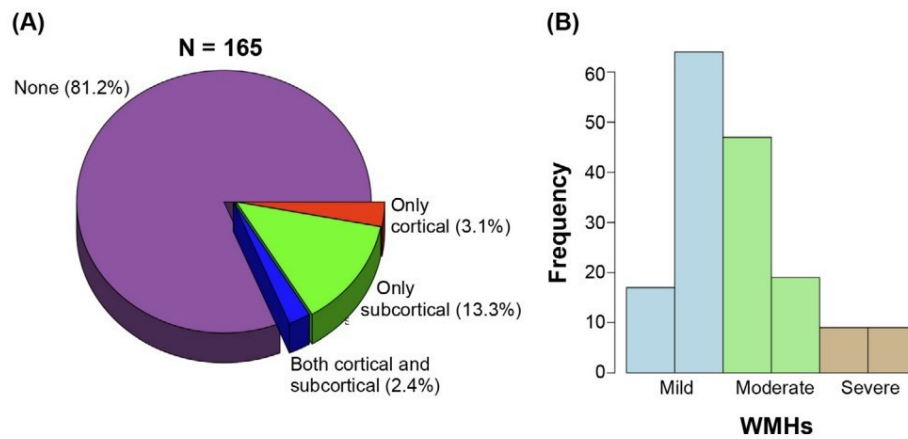
Figure 16. shows the pie chart (A) of the proportions of various distributions of visually rated infarcts within the whole multinational DLB cohort showing that almost 19% of DLB patients have cerebral infarcts typically in a subcortical localization; and (B) colour-coded frequencies of WHM severity 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).
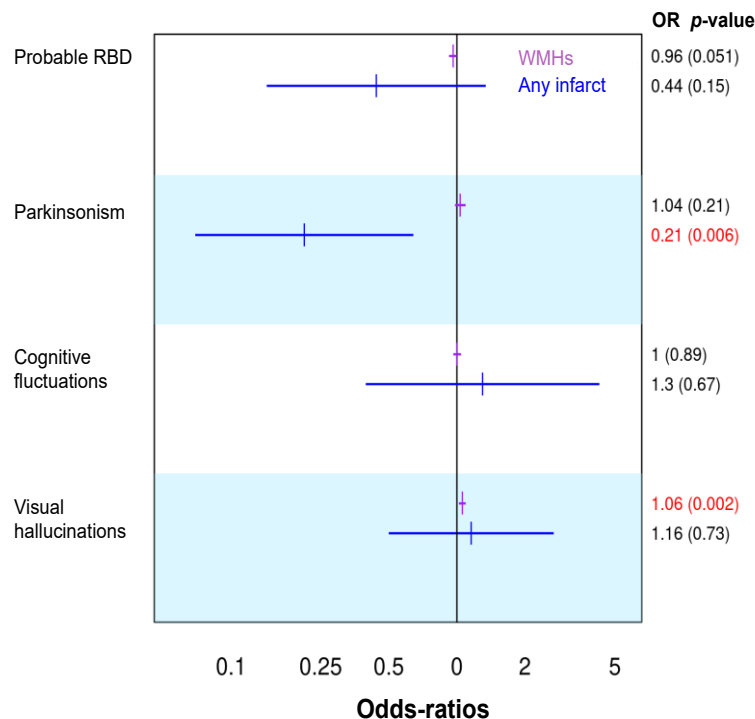
Figure 17. shows the associations among various cerebrovascular pathologies, WMH or infarcts, and their associations with the DLB core clinical features expressed as odds-ratios (Ferreira et al., 2021). Higher WMH burden is significantly associated with a higher frequency of visual hallucinations and lower frequency of RBD (trend). More infarct, interestingly, were associated with lower frequency of parkinsonism.

5. Discussion

5.1. Study I

We showed that the impairment of the world-centred (allocentric) spatial navigation (SN) strategy is associated with the right hippocampal atrophy in real space and in the two-dimensional computer representation of real space. This association was strongest in MCI and full-blown AD dementia individuals. Even after correcting for whole brain and left hippocampal atrophy and demographic factors, right hippocampus atrophy was crucial to allocentric SN dysfunction. The right hippocampus is a critical actor in the allocentric SN, as shown in animals (Morris et al., 1982) and humans (Astur et al., 2002), but not in AD patients.

Right hippocampal atrophy was associated with allocentric SN impairment in both real-world and computerized SN assessments. Our study shows that the computer-based SN test can be used to clinically and functionally assess early AD patients with hippocampal dysfunction (Hort et al., 2007).

5.2. Study II

In a factor analysis, a data reduction technique, our real-space SN test showed that allocentric and egocentric SN scores loaded on a component distinct from six cognitive processes, including verbal and nonverbal memory, executive and visuospatial function, attention/working memory, and language, and were not intercorrelated. Thus, SN and other, traditional cognitive domains share only a modest varice. We also found no correlation between SN performance and performance on tests on traditional cognitive domains in cognitively normal older adults. Only executive function was associated with allocentric SN in aMCI, who often progress to AD dementia. Verbal memory was associated with egocentric SN. These correlations explained 11% and 9% of SN variation, respectively. In aMCI, left and right hippocampal atrophy was associated with allocentric SN and explained 12% and 26% of the variance in allocentric SN, respectively, adjusting for age, sex, and education. We demonstrated that SN is distinct from other

cognitive domains. In a previous study (Hort et al., 2007), we showed that allocentric SN impairment occurs early in AD at the stage of MCI, and 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). Overall, SN examination helps to characterize cognitive and functional performance in older persons, especially 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. Study III

We examined whether patients with aMCI due to AD and those with full-blown AD dementia have abnormal voice emotional prosody recognition (EPR) compared to cognitively normal peers. EPR scores were correlated with brain volumes and cortical thickness of regions involved in emotional processing, such as the amygdala, temporal pole (Olson et al., 2007), rostral and caudal anterior cingulate, and superior temporal sulcus (Watson et al., 2014), with respect to a global cognitive status approximated by MMSE score. Patients with aMCI due to AD and full-blown AD patients reached lower EPR scores than normal older controls (Bush et al., 2000), and AD dementia patients scored even worse on EPR than aMCI due to AD patients. EPR score was moderately to strongly associated with caudal anterior cingulate thickness, temporal pole volume, and superior temporal sulcus thickness: the structures which are both involved in emotional processing and in AD progression. Receiver under the operating curve discrimination analysis showed that EPR can differentiate between controls versus patients (AD dementia and aMCI combined), and even between aMCI versus AD dementia patients. Thus, EPR could be used to stage AD by assessing social and communication abilities, which are important for daily living but typically omitted in neuropsychological tests (Hasson-Ohayon et al., 2017). Our findings may inform the social management of AD and studies targeted at caregiver relief.

5.4. Study IV

20–40% of clinically normal (CN) older persons have a high amyloid load on PET (Jansen et al., 2015). Amyloid accumulation may increase the risk of MCI (Villemagne et al., 2011) and dementia (Leal et al., 2017). However, amyloid PET is relatively expensive and invasive, and has a limited availability. MRI-based indicators of amyloid accumulation, however are more affordable and more accessible. We assessed a large population-based sample of 594 cognitively unimpaired older adults to show that MRS, a common MRI technique, can predict a higher rate of amyloid accumulation on serial PET. Taking into account age at baseline, sex, and APOE4 status, we found 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 higher mI/Cr ratio (a marker of glial activation and inflammation) were associated with a higher rate of amyloid accumulation. APOE4 cognitively unimpaired carriers accumulated amyloid faster than non-carriers. This was the first study to show that APOE4 affects amyloid accumulation over time in clinically normal people. However, APOE4 status had no effect on the association between baseline metabolite levels and amyloid accumulation over time. MRS metabolites and APOE4 are likely independently related to the amyloid accumulation. Future research should standardize and harmonize multi-site MRS acquisition. Additionally, longitudinal MRS studies should address the temporal sequence of MRS metabolites and amyloid accumulation.

5.5. Studies V-X: Necessity for multimodality imaging in DLB

We have conducted several imaging studies to explore Lewy body pathophysiology from prodromal DLB (MCI with LB features) to full-blown DLB to disentangle the LB- and AD-related imaging findings and to understand how the overlapping pathology impacts DLB patients' clinical phenotype.

DLB shows less atrophy in MTL structures on MRI than AD where MTL atrophy

is a typical finding (Jack et al., 2002). Likely because several previous, typically cross- sectional clinical studies included also DLB patients with mixed pathology, they often reported similar MTL atrophy between AD and DLB groups. The autopsy- confirmed longitudinal study with autopsy confirmation was missing. In our studyV (Nedelska et al., 2015), patients with pathologically "pure" LB who were premortem diagnosed with DLB showed decreased brain atrophy rates globally and regionally in the amygdala and hippocampus, similar to controls. However, pathologically mixed DLB with AD showed profound atrophy rates globally and in MTL structures, similar to "pure" AD. Autopsy confirmed DLB with mixed pathology clinically progressed faster and decreased faster on measures of cognition. The evidence from this study was included in the Fourth report of DLB consortium criteria for diagnosis and management of DLB (McKeith et al., 2017).

Brain white matter (WM) has been less studied in DLB patients, and previous findings showed equivocal findings of wide-spread patterns of impaired microintegrity of WM (Watson et al., 2012). Overlapping AD pathology in DLB may impact the WM microstructure, however. Thus, in our study VI. (Nedelska, Schwarz, et al., 2015), we utilized DTI, FDG PET, and amyloid PET to quantify the influence of AD pathology on WM microstructure and compare the WM findings to changes in cortex of DLB patients. Using DTI, we demonstrated a relatively focal, well-defined impairment in WM area bordering posterior parietal, occipital, and temporal lobes. This circumscribed region of WM is a "crossroads" where superior and inferior longitudinal fascicles travel through and are involved in "what" and "where" information processing (Mesulam, 1998). We found a borderline association between WM microstructure impairment in this region and cognitive fluctuations and visual hallucinations in DLB patients, likely due to a smaller sample size. DLB-specific WM impairment was unaffected by PET amyloid load. Finally, WM impairment overlapped with glucose metabolism in the adjacent cerebral cortex, which may help to understand the mechanisms

underlying the cognitive fluctuations and visual hallucinations in DLB.

Cingulate island sign (CIS) is another well-established imaging biomarker of DLB (Lim et al., 2009). FDG-PET, which is less accessible, more expensive and more invasive than MRI, can visualize the CIS sign. In study VII, we used noninvasive perfusion MRI to evaluate CIS and cortical perfusion patterns in DLB, using the notion that brain glucose metabolism is closely associated with blood perfusion. FDG PET and perfusion MRI correlated well for CIS visualization and quantification. Even though some DLB patients had AD co-pathology, perfusion MRI CIS could identify AD from DLB with over 80% accuracy. We confirmed our hypothesis that AD co-pathology decreases CIS using tau-PET. When FDG PET is unavailable, perfusion MRI may provide a cheaper, less invasive, and more accessible alternative to CIS examination in DLB.

In study VIII, we used serial amyloid PET to track longitudinal amyloid accumulation as a function of baseline amyloid load and time in DLB patients (Nedelska et al., 2019). The amyloid accumulation curve was a sigmoid, with gradual acceleration in the rate of accumulation followed by the decrease in the rate and then plateau. Amyloid accumulation curve in DLB resembled the amyloid accumulation AD continuum's (Jack; Villemagne, 2011). In DLB patients, amyloid accumulation was associated with longitudinal functional decline and cognitive worsening, unlike prior cross-sectional investigations (Donaghy et al., 2013). Based on our findings and sample size calculations, our study also suggested that some DLB patients may benefit from the anti-amyloid biologic therapies in the future.

Recently, research in DLB has been focused on prodromal stages (MCI with LB features) to facilitate timely diagnosis and interventions. McKeith et al. (2020) developed prodromal DLB diagnosis criteria intended for research purposes. Prodromal DLB diagnosis relies on REM sleep behavior disorder, cardiac MIBG, DaT scan, quantitative EEG, structural MRI, and molecular imaging to identify overlapping AD pathology. However, longitudinal study on these biomarkers during

the prodromal period have been missing. Thus, in study IX (Kantarci et al., 2022), we examined baseline cross-sectional and longitudinal regional atrophy and rates of atrophy in prodromal MCI patients with core LB characteristics, some of whom have died and were autopsy-confirmed to have LB. We demonstrated that the nucleus basalis of Meynert (NBM), a major cholinergic nukleus supplementing acetylcholine into almost the entire neocortex atrophies early on and that other brain regions undergo perhaps secondarily to the acetylcholine deprivation. While cross-sectional regional atrophy was more focused and located to MTL in prodromal DLB, possibly also due to a degree of AD co-pathology, longitudinal rates of atrophy showed a wide-spread atrophy pattern across vast cortical regions that receive cholinergic inputs from NBM. Our findings have implications for understanding the early, prodromal stages of DLB, and support the administration of AChEI to prodromal DLB patients in MCI stage, whereas insurance companies have paid only for the medication to patients with full-blown dementia, arguing by non-existent randomized clinical trials in MCI due to LBD.

Finally, cerebrovascular disease in DLB patients is clinically important but understudied. In our last study (Ferreira et al., 2021), we showed 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 and can obscure the clinical manifestation of core DLB features, making diagnosis more difficult. In DLB, cerebrovascular disease contributes to the cognitive decline and regional brain atrophy. Thus, treating cerebrovascular comorbidity in DLB is crucial.

6. Conclusion

This thesis investigated how morphometric and metabolic brain changes derived from multimodality imaging affect clinical and cognitive impairment in AD and DLB using structural, microstructural, and perfusion MRI and molecular PET approaches. These imaging approaches were selected to quantify amyloid and tau accumulation and degree of neurodegeneration in patients' brains. In first aim, our objective was to assess less examined flavors of cognition, behavior, and daily functioning such as spatial navigation and social cognition using experimental tests different from established pencil-and-paper neuropsychological test. However, established neuropsychological tests targeted at domains such as memory, executive functions, language etc were administered to assess cognitive profiles of our participants from a standard cognitive domain perspective.

In our second aim, using a non-invasive and affordable method of brain MRS to measure selected brain metabolites, we predicted the increase in brain amyloid accumulation by amyloid PET in clinically unimpaired older participants who may be at increased risk of cognitive impairment and dementia.

In our third aim, we used a variety of multimodality imaging techniques to better understand the pathophysiology of DLB which often coexists with addition AD-related co-pathology. These mixed DLB/AD pathologies cause faster clinical disease progression and shorter survival of the DLB patients and additional burden to caregivers.

Our findings alltogether demonstrate the crucial role of brain imaging in understanding the pathogenesis of AD and DLB and associated clinical, cognitive, and behavioral impairment.

7. Summary

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 SN or poorer social and nonverbal communication, putting further strain on patients and families. Using human analogue of Morris water maze, we showed that the right hippocampus is necessary for world-centred SN, particularly in context of cognitive impairment due to with AD. Because hippocampal atrophy is well-established imaging biomarker of early AD, the SN tests could be used as affordable and reproducible enrichment to standard neuropsychology testing. We showed that SN 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 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, the research of this thesis has shifted to 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 individuals at highest risk of cognitive decline. Amyloid PET is relatively expensive and not widely available. We showed that measurement of certain brain metabolites using non-invasive and affordable MR spectroscopy 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 ever, 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 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

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 demencí, přičemž skóre testu prozódie korelovalo s atrofií mozkových struktur důležitých jak pro zpracování emocí, tak pro AD. Podle skóre testu prozódie bylo možné odlišit prodromální AD od kontrol i od pacientů s již rozvinutou demencí. V další práci jsem se zabývala molekulárním zobrazením amyloidu pomocí PET, již zavedeného biomarkeru AD. Kvůli plánování účinných intervencí potřebujeme cílit na osoby s preklinickou AD a snažit se najít způsob, jak rozpoznat ty, kteří se kognitivně skutečně zhorší, 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 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 tato dynamika ukládání amyloidu u DLB je velmi podobná té u AD. 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 pochopení významné role amyloidové a tau ko-patologie, která ovlivňuje DLB fenotyp, prognózu a přežití pacientů s DLB.

9. References

1. Adolphs, R., Damasio, H., & Tranel, D. (2002). Neural systems for recognition of emotional prosody: a 3-D lesion study. *Emotion*, *2*(1), 23-51.

2. Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers. Dement.* 7, 270–9.

3. Amlerova, J., Laczo, J., Nedelska, Z., Laczo, M., Vyhnalek, M., Zhang, B., et al. (2022). Emotional prosody recognition is impaired in Alzheimer's disease. *Alzheimers Res Ther*, *14*(1), 50.

4. Astur, R. S., Taylor, L. B., Mamelak, A. N., Philpott, L., & Sutherland, R. J. (2002). Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. *Behavioural brain research*, *132*(1), 77- 84.

5. Barber, R., Ballard, C., McKeith, I. G., Gholkar, A., & O'Brien, J. T. (2000). MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. *Neurology*, *54*(6), 1304-1309.

6. Bates, S. L., & Wolbers, T. (2014). How cognitive ageing affects multisensory integration of navigational cues. *Neurobiol Ageing*, *35*(12), 2761-2769.

7. Braak, H., and Braak, E. (1995). Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol. Aging* 16, 271–284.

8. Bobinski, M., de Leon, M. J., Convit, A., De Santi, S., Wegiel, J., Tarshish, C. Y., et al. (1999). MRI of entorhinal cortex in mild Alzheimer's disease. *Lancet*, *353*(9146), 38-40.

9. Boeve, B. F., Silber, M. H., Ferman, T. J., Lin, S. C., Benarroch, E. E., Schmeichel, A. M., et al. (2013). Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep medicine*.

10. Burton, E. J., McKeith, I. G., Burn, D. J., Williams, E. D., & O'Brien, J. T. (2004). Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. *Brain : a journal of neurology*, *127*(Pt 4), 791-800.

11. Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in cognitive sciences*, *4*(6), 215-222.

12. Carmichael, O., & Lockhart, S. (2012). The role of diffusion tensor imaging in the study of cognitive ageing. *Curr Top Behav Neurosci*, *11*, 289-320.

13. Chen, Q., Qing, Z., Jin, J., Sun, Y., Chen, W., Lu, J., et al. (2021). Ego- and allo-network disconnection underlying spatial disorientation in subjective cognitive decline. *Cortex; a journal devoted to the study of the nervous system and behavior*, *137*, 35-48.

14. Cerman J., Andel R., Laczo J., Vyhnalek M., Nedelska Z., Mokrisova I., et al. Subjective Spatial Navigation Complaints - A Frequent Symptom Reported by Patients with Subjective Cognitive Decline, Mild Cognitive Impairment and Alzheimer's Disease. *Curr Alzheimer Res*. 2018;15(3):219-228.

15. DeCarli, C., Frisoni, G. B., Clark, C. M., Harvey, D., Grundman, M., Petersen, R. C., et al. & Alzheimer's Disease Cooperative Study, G. (2007). Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Arch Neurol*, *64*(1), 108-115.

16. deIpolyi, A. R., Rankin, K. P., Mucke, L., Miller, B. L., & Gorno-Tempini, M. L. (2007). Spatial cognition and the human navigation network in AD and MCI. *Neurology*, *69*(10), 986-997.

17. Detre, J. A., Wang, J., Wang, Z., & Rao, H. (2009). Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. *Current opinion in neurology*, *22*(4), 348-355.

18. Donaghy, P., Thomas, A. J., & O'Brien, J. T. (2013). Amyloid PET Imaging in Lewy Body Disorders. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*.

19. Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., et al. (2003). Cellular networks underlying human spatial navigation. *Nature*, *425*(6954), 184-188.

20. Elferink, M. W., van Tilborg, I., & Kessels, R. P. (2015). Perception of emotions in mild cognitive impairment and Alzheimer's dementia: does intensity matter? *Transl Neurosci*, *6*(1), 139-149.

21. Ferreira, D., Nedelska, Z., Graff-Radford, J., Przybelski, S. A., Lesnick, T. G., Schwarz, C. G., et al. (2021). Cerebrovascular disease, neurodegeneration, and clinical phenotype in dementia with Lewy bodies. *Neurobiol Ageing*, *105*, 252-261.

22. Gallagher, M., & Chiba, A. A. (1996). The amygdala and emotion. *Curr Opin Neurobiol*, *6*(2), 221-227.

23. Glanville, N. T., Byers, D. M., Cook, H. W., Spence, M. W., & Palmer, F. B. (1989). Differences in the metabolism of inositol and phosphoinositides by cultured cells of neuronal and glial origin. *Biochimica et biophysica acta*, *1004*(2), 169-179.

24. Gazova, I., Laczo, J., Rubinova, E., Mokrisova, I., Hyncicova, E., Andel, R., Vyhnalek, M., Sheardova, K., Coulson, E. J., & Hort, J. (2013). Spatial navigation in young versus older adults. *Front Ageing Neurosci*, *5*, 94.

25. Hasson-Ohayon, I., Mashiach-Eizenberg, M., Arnon-Ribenfeld, N., Kravetz, S., & Roe, D. (2017). Neuro-cognition and social cognition elements of social functioning and social quality of life. *Psychiatry research*, *258*, 538-543.

26. Hort, J., Laczo, J., Vyhnalek, M., Bojar, M., Bures, J., & Vlcek, K. (2007). Spatial navigation deficit in amnestic mild cognitive impairment [Research Support, Non-U.S. Gov't]. *Proceedings of the National Academy of Sciences of*

the United States of America, *104*(10), 4042-4047.

27. Huang, W., Alexander, G. E., Chang, L., Shetty, H. U., Krasuski, J. S., Rapoport, S. I., et al. (2001). Brain metabolite concentration and dementia severity in Alzheimer's disease: a (1)H MRS study. *Neurology*, *57*(4), 626-632.

28. Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement.* 14, 535–562.

29. Jack, C. R., Jr., Dickson, D. W., Parisi, J. E., Xu, Y. C., Cha, R. H., O'Brien, P. C., Edland, S. D., et al. (2002). Antemortem MRI findings correlate with hippocampal neuropathology in typical ageing and dementia. *Neurology*, *58*(5), 750-757.

30. Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R., et al. (2015). Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA : the journal of the American Medical Association*, *313*(19), 1924-1938.

31. Kantarci, K., Murray, M. E., Schwarz, C. G., Reid, R. I., Przybelski, S. A., Lesnick, T., et al. (2017). White-matter integrity on DTI and the pathologic stageing of Alzheimer's disease. *Neurobiol Ageing*, *56*, 172-179.

32. Kantarci, K., Nedelska, Z., Chen, Q., Senjem, M. L., Schwarz, C. G., Gunter, J. L., et al. (2022). Longitudinal atrophy in prodromal dementia with Lewy bodies points to cholinergic degeneration. *Brain Commun*, *4*(2), fcac013.

33. Kosaka, K. (1978). Lewy bodies in cerebral cortex, report of three cases. *Acta neuropathologica*, *42*(2), 127-134.

34. Laczó, J., Andel, R., Vyhnalek, M., Vlcek, K., Magerova, H., Varjassyova, A., et al. (2012). From Morris Water Maze to Computer Tests in the Prediction of Alzheimer's Disease. *Neurodegener. Dis* 10, 153–157.

35. Laczo, J., Vlcek, K., Vyhnalek, M., Vajnerova, O., Ort, M., Holmerova, I., et al. (2009). Spatial navigation testing discriminates two types of amnestic mild cognitive impairment. *Behav Brain Res*, *202*(2), 252-259.

36. Laczo, J., Andel, R., Vyhnalek, M., Vlcek, K., Nedelska, Z., Matoska, V., Gazova, I., Mokrisova, I., Sheardova, K., & Hort, J. (2014). APOE and spatial navigation in amnestic MCI: results from a computer-based test. *Neuropsychology*, *28*(5), 676-684.

37. Leal, S. L., Landau, S. M., Bell, R. K., & Jagust, W. J. (2017). Hippocampal activation is associated with longitudinal amyloid accumulation and cognitive decline. *Elife*, *6*.

38. Lemstra, A. W., de Beer, M. H., Teunissen, C. E., Schreuder, C., Scheltens, P., van der Flier, W. M., & Sikkes, S. A. (2017). Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*, *88*(2), 113-118.

39. Lim, S. M., Katsifis, A., Villemagne, V. L., Best, R., Jones, G., Saling, M., et al. (2009). The 18F-FDG PET cingulate island sign and comparison to 123I-beta- CIT SPECT for diagnosis of dementia with Lewy bodies. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, *50*(10),

1638-1645.

40. Madsen, P. L., Hasselbalch, S. G., Hagemann, L. P., Olsen, K. S., Bulow, J., Holm, S.,et al. (1995). Persistent resetting of the cerebral oxygen/glucose uptake ratio by brain activation: evidence obtained with the Kety-Schmidt technique. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*, *15*(3), 485-491.

41. Maguire, E., Burgess, N., Donnett, J., Frackowiak, R., Frith, C., and O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science* 280, 921–924.

42. McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., et al. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88-100.

43. McKeith, I. G., Ferman, T. J., Thomas, A. J., Blanc, F., Boeve, B. F., Fujishiro, H., et al. (2020). Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology*, *94*(17), 743-755.

44. McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers. Dement.* 7, 263–269.

45. Merdes, A. R., Hansen, L. A., Jeste, D. V., Galasko, D., Hofstetter, C. R., Ho, G. J., et al. (2003). Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies *Neurology*, *60*(10), 1586-1590.

46. Mesulam, M. M., Mufson, E. J., Levey, A. I., and Wainer, B. H. (1983). Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J. Comp. Neurol.* 214, 170– 1971.

47. Moffat, S. D., Kennedy, K. M., Rodrigue, K. M., & Raz, N. (2007). Extrahippocampal contributions to age differences in human spatial navigation. *Cerebral cortex*, *17*(6), 1274-1282.

48. Morris, R. G., Garrud, P., Rawlins, J. N., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, *297*(5868), 681-683.

49. Mukherjee, A., Biswas, A., Roy, A., Biswas, S., Gangopadhyay, G., & Das, S. K. (2017). Behavioural and Psychological Symptoms of Dementia: Correlates and Impact on Caregiver Distress. *Dementia and geriatric cognitive disorders extra*, *7*(3), 354-365.

50. Nedelska, Z., Andel, R., Laczo, J., Vlcek, K., Horinek, D., Lisy, J., Sheardova, K., Bures, J., & Hort, J. (2012). Spatial navigation impairment is proportional to right hippocampal volume. *Proc Natl Acad Sci U S A*, *109*(7), 2590-2594.

51. Nedelska, Z., Ferman, T. J., Boeve, B. F., Przybelski, S. A., Lesnick, T. G., Murray, M. E., et al. (2015). Pattern of brain atrophy rates in autopsy-confirmed

dementia with Lewy bodies. *Neurobiol Ageing*, *36*(1), 452-461.

52. Nedelska, Z., Przybelski, S. A., Lesnick, T. G., Schwarz, C. G., Lowe, V. J., Machulda, M. M., et al. (2017). (1)H-MRS metabolites and rate of beta-amyloid accumulation on serial PET in clinically normal adults. *Neurology*, *89*(13), 1391-1399.

53. Nedelska, Z., Senjem, M. L., Przybelski, S. A., Lesnick, T. G., Lowe, V. J., Boeve, B. F., et al. (2018). Regional cortical perfusion on arterial spin labeling MRI in dementia with Lewy bodies: Associations with clinical severity, glucose metabolism and tau PET. *Neuroimage Clin*, *19*, 939-947.

54. Nedelska, Z., Schwarz, C. G., Boeve, B. F., Lowe, V. J., Reid, R. I., Przybelski, S. A., et al. (2015). White matter integrity in dementia with Lewy bodies: a voxel-based analysis of diffusion tensor imaging. *Neurobiol Ageing*, *36*(6), 2010-2017.

55. Nedelska, Z., Schwarz, C. G., Lesnick, T. G., Boeve, B. F., Przybelski, S. A., Lowe, V. J.,et al. (2019). Association of Longitudinal beta-Amyloid Accumulation Determined by Positron Emission Tomography With Clinical and Cognitive Decline in Adults With Probable Lewy Body Dementia. *JAMA Netw Open*, *2*(12), e1916439.

56. Nelson, P. T., Jicha, G. A., Kryscio, R. J., Abner, E. L., Schmitt, F. A., Cooper, G., et al. (2010). Low sensitivity in clinical diagnoses of dementia with Lewy bodies. *Journal of neurology*, *257*(3), 359-366.

57. Nir, T. M., Jahanshad, N., Villalon-Reina, J. E., Toga, A. W., Jack, C. R., Weiner, M. W., et al., & Alzheimer's Disease Neuroimaging, I. (2013). Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal ageing. *Neuroimage Clin*, *3*, 180-195.

58. Olson, I. R., Plotzker, A., & Ezzyat, Y. (2007). The Enigmatic temporal pole: a review of findings on social and emotional processing. *Brain*, *130*(Pt 7), 1718-1731.

59. Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magn Reson Med*, *36*(6), 893-906.

60. Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S.,et al. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *The New England journal of medicine*, *334*(12), 752-758.

61. Roberts, R. O., Geda, Y. E., Knopman, D. S., Cha, R. H., Pankratz, V. S., Boeve, B. F., et al. (2012). The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Ageing. *Neurology*, *78*(5), 342-351.

62. Rongve, A., Soennesyn, H., Skogseth, R., Oesterhus, R., Hortobagyi, T., Ballard, C., et al. (2016). Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. *BMJ open*, *6*(2), e010357.

63. Santamaria-Garcia, H., Baez, S., Gomez, C., Rodriguez-Villagra, O., Huepe, D., Portela, M., et al. (2020). The role of social cognition skills and social determinants of health in predicting symptoms of mental illness. *Translational psychiatry*, *10*(1), 165.

64. Schoenmakers, B., Buntinx, F., & De Lepeleire, J. (2009). The relation between care giving and the mental health of caregivers of demented relatives: a cross- sectional study. *Eur J Gen Pract*, *15*(2), 99-106.

65. Schneider, J. A., Arvanitakis, Z., Bang, W., & Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*, *69*(24), 2197-2204.

66. Sheardova, K., Vyhnalek, M., Nedelska, Z., Laczo, J., Andel, R., Marciniak, R., et al. (2019). Czech Brain Ageing Study (CBAS): prospective multicentre cohort study on risk and protective factors for dementia in the Czech Republic. *BMJ open*, *9*(12), e030379.

67. Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *A. lzheimers. Dement.* 7, 280–292.

68. Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). Alpha-synuclein in Lewy bodies [Letter]. *Nature*, *388*(6645), 839-840.

69. Thal, D. R., Rüb, U., Orantes, M., and Braak, H. (2002). Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 58, 1791–1800.

70. Villemagne, V. L., Pike, K. E., Chetelat, G., Ellis, K. A., Mulligan, R. S., Bourgeat, P., et al. (2011). Longitudinal assessment of Abeta and cognition in ageing and Alzheimer disease. *Annals of neurology*, *69*(1), 181-192.

71. Villemagne, V., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., et al, Australian Imaging, B., & Lifestyle Research, G. (2013). Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*, *12*(4), 357-367.

72. Voevodskaya, O., Sundgren, P. C., Strandberg, O., Zetterberg, H., Minthon, L., Blennow, K., et al., & Swedish Bio, F. s. g. (2016). Myo-inositol changes precede amyloid pathology and relate to APOE genotype in Alzheimer disease. *Neurology*, *86*(19), 1754-1761.

73. Watson, R., Latinus, M., Noguchi, T., Garrod, O., Crabbe, F., & Belin, P. (2014). Crossmodal adaptation in right posterior superior temporal sulcus during face-voice emotional integration. *J Neurosci*, *34*(20), 6813-6821.

74. Weniger, G., Ruhleder, M., Lange, C., Wolf, S., and Irle, E. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. *Neuropsychologia* 49, 518–527.

75. Whitwell, J. L., Jack, C. R., Jr., Parisi, J. E., Knopman, D. S., Boeve, B. F., Petersen, R. C., et al. (2007). Rates of cerebral atrophy differ in different degenerative pathologies. *Brain : a journal of neurology*, *130*(Pt 4), 1148-1158.

76. Wiener, J. M., Caroll, D., Moeller, S., Bibi, I., Ivanova, D., Allen, P., et al. (2020). A novel virtual-reality-based route-learning test suite: Assessing the effects of cognitive aging on navigation. *Behav. Res. Methods* 52, 630–640.

77. Williams, D. S., Detre, J. A., Leigh, J. S., & Koretsky, A. P. (1992). Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc Natl Acad Sci U S A*, *89*(1), 212-216.

78. Wolbers, T., and Wiener, J. M. (2014). Challenges for identifying the neural mechanisms that support spatial navigation: the impact of spatial scale. *Front. Hum. Neurosci.* 8.

79. Yoshita, M., Arai, H., Arai, H., Arai, T., Asada, T., Fujishiro, H., et al. (2015). Diagnostic accuracy of 123I-meta-iodobenzylguanidine myocardial scintigraphy in dementia with Lewy bodies: a multicenter study. *PloS one*, *10*(3), e0120540.

10. Overview of author's publications and activities

Dr. Nedelska's cumulative impact factor is around 287.5, H-index is 21, 1098 citations (WOS)

10.1. Original papers 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*

7. **Nedelska Z**, Senjem ML, Przybelski SA, Lesnick TG, Lowe VJ, Boeve BF, Arani A, Vemuri P, Graff-Radford J, Ferman TJ, Jones DT, Savica R, Knopman DS, Petersen RC, Jack CR, Kantarci K. Regional cortical perfusion on arterial spin labeling MRI in dementia with Lewy bodies: Associations with clinical severity, glucose metabolism and tau PET. *NeuroImage Clin.* 2018 Jun 19;19:939-947.**IF 4.891**

8. **Nedelska Z**, Schwarz CG, Lesnick TG, Boeve BF, Przybelski SA, Lowe VJ, Kremers WK, Gunter JL, Senjem ML, Graff-Radford J, Ferman TJ, Fields JA, Knopman DS, Petersen RC, Jack CR Jr, Kantarci K. Association of Longitudinal β-Amyloid Accumulation Determined by Positron Emission Tomography With Clinical and Cognitive Decline in Adults With Probable Lewy Body Dementia. *JAMA Netw Open.* 2019 Dec 2;2(12):e1916439.16439. ***IF 13.353***

9. Kantarci K, **Nedelska Z***, Chen Q, Senjem ML, Schwarz CG, Gunter JL, Przybelski SA, Lesnick TG, Kremers WK, Fields JA, Graff-Radford J, Savica R, Jones D, Botha H, Knopman DS, Lowe V, Graff-Radford NR, Murray MM, Dickson DW, Reichard RR, Jack CR Jr, Petersen RC, Ferman TJ, Boeve BF. Longitudinal atrophy in prodromal dementia with Lewy bodies points to cholinergic degeneration. *Brain Commun.* 2022 Feb 7;4(2):fcac013. ***IF not available yet as it is a new journal. The current derived metrics is 4.4 but escalation is expected. It is a sister journal to Brain with IF 15.255***

10. Ferreira D, **Nedelska Z**, Graff-Radford J, Przybelski SA, Lesnick TG, Schwarz CG, Botha H, Senjem ML, Fields JA, Knopman DS, Savica R, Ferman TJ, Graff-Radford NR, Lowe VJ, Jack CR, Petersen RC, Lemstra AW, van de Beek M, Barkhof F, Blanc F, Loureiro de Sousa P, Philippi N, Cretin B, Demuynck C, Hort J, Oppedal K, Boeve BF, Aarsland D, Westman E, Kantarci K. Cerebrovascular disease, neurodegeneration, and clinical phenotype in dementia with Lewy bodies. *Neurobiol Ageing.* 2021 Sep;105:252-261. ***IF 5.133***

10.2. Original publications which are related the dissertation: papers with IF

11. Kerbler GM, **Nedelska Z**, Fripp J, Laczó J, Vyhnalek M, Lisý J, Hamlin AS, Rose S, Hort J, Coulson EJ. Basal Forebrain Atrophy Contributes to Allocentric Navigation Impairment in Alzheimer's Disease Patients. *Front Ageing Neurosci.* 2015 Sep 28;7:185. *IF 4.348*

12. **Nedelska Z**, Kantarci K. Basis of cingulate island sign may differ in dementia with lewy bodies and posterior cortical atrophy. *Mov Disord.* 2019 May;34(5):761-762. *IF 8.679*

13. **Nedelska Z**, Josephs KA, Graff-Radford J, Przybelski SA, Lesnick TG, Boeve BF, Drubach DA, Knopman DS, Petersen RC, Jack CR Jr, Lowe VJ, Whitwell JL, Kantarci K. [18] F-AV-1451 uptake differs between dementia with lewy bodies and posterior cortical atrophy. *Mov Disord.* 2019 Mar;34(3):344-352. *IF 8.679*

14. Laczó J, Andel R, Vyhnalek M, Matoska V, Kaplan V, **Nedelska Z**, Lerch O, Gazova I, Moffat SD, Hort J. The effect of TOMM40 on spatial navigation in amnestic mild cognitive impairment. *Neurobiol Ageing.* 2015 Jun;36(6):2024-33. *IF 5.113*

15. Gazova I, Vlcek K, Laczó J, **Nedelska Z**, Hyncicova E, Mokrisova I, Sheardova K, Hort J. Spatial navigation-a unique window into physiological and pathological ageing. *Front Ageing Neurosci.* 2012 Jun 21;4:16. *IF 5.224*

16. Laczó J, Andel R, Vyhnalek M, Vlcek K, Magerova H, Varjassyova A, **Nedelska Z**, Gazova I, Bojar M, Sheardova K, Hort J. From Morris Water Maze to computer tests in the prediction of Alzheimer's disease. *Neurodegener Dis.* 2012;10(1-4):153-7. *IF 3.454*

17. Laczó J, Andel R, Vyhnalek M, Vlcek K, **Nedelska Z**, Matoska V, Gazova I, Mokrisova I, Sheardova K, Hort J APOE and spatial navigation in amnestic MCI: results from a computer-based test. *Neuropsychology.* 2014 Sep;28(5):676-684. *IF 3.269*

18. Mokrisova I, Laczo J, Andel R, Gazova I, Vyhnalek M, **Nedelska Z**, Levcik D, Cerman J, Vlcek K, Hort J. Real-space path integration is impaired in

Alzheimer's disease and mild cognitive impairment. *Behav Brain Res*. 2016 Jul 1;307:150-8. ***IF 3.173***

19. Lerch O, Laczó M, Vyhnálek M, **Nedelská Z**, Hort J, Laczó J. APOEε4 Allele Moderates the Association Between Basal Forebrain Nuclei Volumes and Allocentric Navigation in Older Adults Without Dementia. *J Alzheimers Dis.* 2022;86(1):155-171. ***IF 4.16***

20. Laczó J, Cechova K, Parizkova M, Lerch O, Andel R, Matoska V, Kaplan V, Matuskova V, **Nedelska Z**, Vyhnalek M, Hort J. The Combined Effect of APOE and BDNF Val66Met Polymorphisms on Spatial Navigation in Older Adults.*J Alzheimers Dis*. 2020;78(4):1473-1492. ***IF 4.472***

21. Parizkova M, Lerch O, Moffat SD, Andel R, Mazancova AF, **Nedelska Z**, Vyhnalek M, Hort J, Laczó J. The effect of Alzheimer's disease on spatial navigation strategies. *Neurobiol Ageing.* 2018 Apr;64:107-115. ***IF 4.398***

22. Cerman J, Andel R, Laczo J, Vyhnalek M, **Nedelska Z**, Mokrisova I, Sheardova K, Hort J. Subjective Spatial Navigation Complaints - A Frequent Symptom Reported by Patients with Subjective Cognitive Decline, Mild Cognitive Impairment and Alzheimer's Disease. *Curr Alzheimer Res*. 2018;15(3):219-228. ***IF 3.211***

23. Vyhnalek M, Nikolai T, Andel R, **Nedelska Z**, Rubínová E, Marková H, Laczó J, Bezdicek O, Sheardova K, Hort J.Neuropsychological correlates of hippocampal atrophy in memory testing in nondemented older adults. *J Alzheimers Dis*. 2014;42 Suppl 3:S81-90. ***IF 4.151***

24. Matuskova V, Ismail Z, Nikolai T, Markova H, Cechova K, **Nedelska Z**, Laczó J, Wang M, Hort J, Vyhnalek M. Mild Behavioral Impairment Is Associated With Atrophy of Entorhinal Cortex and Hippocampus in a Memory Clinic Cohort. *Front Ageing Neurosci*. 2021 May 24;13:643271. ***IF 5.702***

25. Markova H, Fendrych Mazancova A, Jester DJ, Cechova K, Matuskova V, Nikolai T, **Nedelska Z**, Uller M, Andel R, Laczó J, Hort J, Vyhnalek M. Memory Binding Test and Its Associations With Hippocampal Volume Across

the Cognitive Continuum Preceding Dementia. *Assessment.* 2022 Jan 13:10731911211069676. ***IF 4.282***

26. Nemy M, Cedres N, Grothe MJ, Muehlboeck JS, Lindberg O, **Nedelska Z**, Stepankova O, Vyslouzilova L, Eriksdotter M, Barroso J, Teipel S, Westman E, Ferreira D.Cholinergic white matter pathways make a stronger contribution to attention and memory in normal ageing than cerebrovascular health and nucleus basalis of Meynert. *Neuroimage.* 2020 May 1;211:116607. ***IF 6.556***

27. Ferreira D, Przybelski SA, Lesnick TG, Lemstra AW, Londos E, **Nedelska Z**, Schwarz CG, Graff-Radford J, Senjem ML, Fields JA, Knopman DS, Savica R, Ferman TJ, Graff-Radford NR, Lowe VJ, Jack CR Jr, Petersen RC, Mollenhauer B, Garcia-Ptacek S, Abdelnour C, Hort J, Bonanni L, Oppedal K, Kramberger MG, Boeve BF, Aarsland D, Westman E, Kantarci K. β-Amyloid and tau biomarkers and clinical phenotype in dementia with Lewy bodies. *Neurology.* 2020 Dec 15;95(24):e3257-e3268. ***IF 9.910***

28. Abdelnour C, Ferreira D, Oppedal K, Cavallin L, Bousiges O, Wahlund LO, **Nedelska Z**, Hort J, Padovani A, Pilotto A, Bonanni L, Kramberger MG, Boada M, Westman E, Pagonabarraga J, Kulisevsky J, Blanc F, Aarsland D. The combined effect of amyloid-β and tau biomarkers on brain atrophy in dementia with Lewy bodies. Neuroimage Clin. 2020;27:102333.*Neuroimage:Clinical* ***IF 4.891***

29. Laczó M, Martinkovic L, Lerch O, Wiener JM, Kalinova J, Matuskova V, **Nedelska Z**, Vyhnalek M, Hort J, Laczó J. Different Profiles of Spatial Navigation Deficits In Alzheimer's Disease Biomarker-Positive Versus Biomarker-Negative Older Adults With Amnestic Mild Cognitive Impairment. *Front Ageing Neurosci*. 2022 Jun 2;14:886778 ***IF 5.702***

30. Oltra J, Habich A, Schwarz CG, **Nedelska Z**, Przybelski SA, Inguanzo A, Diaz-Galvan P, Lowe VJ, Oppedal K, Blanc F, Lemstra AW, Hort J, Padovani A, Rektorova I, Bonanni L, Massa F, Kramberger MG, Taylor JP, Snædal J, Walker Z, Antonini A, Segura B, Junque C, Westman E, Boeve BF, Aarsland D, Kantarci

K, Ferreira D. Sex differences in brain atrophy in dementia with Lewy bodies. Res Sq [Preprint]. 2023 Jan 27:rs.3.rs-2516427. Under review *Alzheimer&Dementia*

31. Gonzalez MC, Tovar-Rios DA, Alves G, Dalen I, Williams-Gray CH, Camacho M, Forsgren L, Bäckström D, Lawson RA, Macleod AD, Counsell CE, Paquet C, De Lena C, Antonio F, Pilotto A, Padovani A, Blanc F, Falup-Pecurariu C, Lewis S, Rejdak K, Papuc E, Hort J, **Nedelska Z**, OBrien J, Bonanni L, Marquié M, Abdelnour C, Alcolea D, Beyer K, Aarsland A, Maple-Grødem J. Cognitive and motor decline in Dementia with Lewy bodies and Parkinson's Disease Dementia. In press, Movement Disorders Clinical Practice 2023. *IF 4.514*

10.3. Papers unrelated to the thesis: papers with IF

32. Sheardova K, Vyhnalek M, **Nedelska Z**, Laczo J, Andel R, Marciniak R, Cerman J, Lerch O, Hort J.Czech Brain Ageing Study (CBAS): prospective multicentre cohort study on risk and protective factors for dementia in the Czech Republic.BMJ Open. 2019 Dec 18;9(12):e030379. *IF 2.496*

33. Nelson ME, Andel R, **Nedelska Z**, Martinkova J, Cechova K, Markova H, Matuskova V, Nikolai T, Lerch O, Parizkova M, Laczo J, Vyhnalek M, Hort J. The Association Between Homocysteine and Memory in Older Adults.*J Alzheimers Dis*. 2021;81(1):413-426 *IF 4.16*

34. Ferretti MT, Martinkova J, Biskup E, Benke T, Gialdini G, **Nedelska Z**, Rauen K, Mantua V, Religa D, Hort J, Santuccione Chadha A, Schmidt R.Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice: Position paper of the Dementia and Cognitive Disorders Panel of the European Academy of Neurology. *Eur J Neurol*. 2020 Jun;27(6):928-943. *IF 6.089*

35. Cechova K, Andel R, Angelucci F, Chmatalova Z, Markova H, Laczó J, Vyhnalek M, Matoska V, Kaplan V, **Nedelska Z**, Ward DD, Hort J. Impact of APOE and

BDNF Val66Met Gene Polymorphisms on Cognitive Functions in Patients with Amnestic Mild Cognitive Impairment. *J Alzheimers Dis.* 2020;73(1):247-257. *IF 4.472*

36. Li W, Zhao H, Qing Z, **Nedelska Z**, Wu S, Lu J, Wu W, Yin Z, Hort J, Xu Y, Zhang B. Disrupted Network Topology Contributed to Spatial Navigation Impairment in Patients With Mild Cognitive Impairment. *Front Ageing Neurosci.* 2021 Jun 3;13:630677. *IF 5.702*

37. Zhang W, Qing Z, Hu Y, Shao M, Lu J, Wang J, Li M, Zhang X, **Nedelska Z**, Hort J, Wang Z, Qiao T, Zhang B.Thalamic Atrophy Plays a Crucial Role in the Effect of Asymptomatic Carotid Stenosis on Cognitive Impairment. *Clin Interv Ageing.* 2020 Nov 6;15:2083-2094. *IF 4.458*

38. Chen Q, Qing Z, Jin J, Sun Y, Chen W, Lu J, Lv P, Liu J, Li X, Wang J, Zhang W, Wu S, Yan X, **Nedelska Z**, Hort J, Zhang X, Zhang B. Ego- and allo-network disconnection underlying spatial disorientation in subjective cognitive decline. *Cortex.* 2021 Apr;137:35-48. *IF 4.644*

39. Chen Q, Wu S, Li X, Sun Y, Chen W, Lu J, Zhang W, Liu J, Qing Z, **Nedelska Z**, Hort J, Zhang X, Zhang B. Basal Forebrain Atrophy Is Associated With Allocentric Navigation Deficits in Subjective Cognitive Decline. *Front Ageing Neurosci.* 2021 Feb 15;13:596025. *IF 5.702*

40. Qing Z, Zhang X, Ye M, Wu S, Wang X, **Nedelska Z**, Hort J, Zhu B, Zhang B.The Impact of Spatial Normalization Strategies on the Temporal Features of the Resting-State Functional MRI: Spatial Normalization Before rs-fMRI Features Calculation May Reduce the Reliability. *Front Neurosci.* 2019 Nov 26;13:1249.*IF 3.5152*

41. Zhang X, Sun Y, Li W, Liu B, Wu W, Zhao H, Liu R, Zhang Y, Yin Z, Yu T, Qing Z, Zhu B, Xu Y, **Nedelska Z**, Hort J, Zhang B; Alzheimer's Disease Neuroimaging Initiative. Characterization of white matter changes along fibers by automated fiber quantification in the early stages of Alzheimer's disease. *Neuroimage Clin.* 2019;22:101723.*IF 5.426*

42. Nie X, Sun Y, Wan S, Zhao H, Liu R, Li X, Wu S, **Nedelska Z**, Hort J, Qing Z, Xu Y, Zhang B. Subregional Structural Alterations in Hippocampus and Nucleus Accumbens Correlate with the Clinical Impairment in Patients with Alzheimer's Disease Clinical Spectrum: Parallel Combining Volume and Vertex-Based Approach. *Front Neurol.* 2017 Aug 15;8:399. **IF 3.552**

43. Qing Z, Li W, **Nedelska Z**, Wu W, Wang F, Liu R, Zhao H, Chen W, Chan Q, Zhu B, Xu Y, Hort J, Zhang B. Spatial Navigation Impairment Is Associated with Alterations in Subcortical Intrinsic Activity in Mild Cognitive Impairment: A Resting-State fMRI Study. *Behav Neurol.* 2017;2017:6364314. **IF 2.088**

44. Wu YF, Wu WB, Liu QP, He WW, Ding H, Nedelska Z, Hort J, Zhang B, Xu Y. Presence of lacunar infarctions is associated with the spatial navigation impairment in patients with mild cognitive impairment: a DTI study. *Oncotarget.* 2016 Nov 29;7(48):78310-78319. **IF 5.168**

45. Ni L, Liu R, Yin Z, Zhao H, **Nedelska Z**, Hort J, Zhou F, Wu W, Zhang X, Li M, Yu H, Zhu B, Xu Y, Zhang B. Aberrant Spontaneous Brain Activity in Patients with Mild Cognitive Impairment and concomitant Lacunar Infarction: A Resting-State Functional MRI Study. *J Alzheimers Dis.* 2016;50(4):1243-54. **IF 4.151**

46. Zhang B, Ni L, Wang F, **Nedelska Z,** et al. Effective doctor-patient communication skills training optimizes functional organization of intrinsic brain architecture: a resting-state functional MRI study. *Journal of Biomedical Research* 2017, **IF 1.93**

47. Geda YE, **Nedelska Z**. Mild cognitive impairment: a subset of minor neurocognitive disorder? *Am J Geriatr Psychiatry.* 2012 Oct;20(10):821-6. **IF 4.131**

48. Nelson M, Andel R, Martinkova J, Cechova K, Markova H, **Nedelska Z**, Vyhnalek M, Hort J. Moderating effect of cognitive reserve on brain integrity and cognitive performance. *2022 Frontiers in Ageing Neuroscience 2022 IF 5.702*

49. Chen Q, Long C, Chen F, Zhu Y, Jiang Y, Lu J, Zhang X, **Nedelska Z**, Hort J, Zhang B. Reconfiguration of brain dynamics underlying spatial deficits in subjective cognitive decline. *Neurobiology of Ageing, in press 2023* **IF 5.133**

50. Chen Q, Chen F, Long C, Zhu Y, Jiang Y, Zhu Z, Lu J, Zhang X; **Nedelska Z**, Hort J, Zhang B.Spatial navigation is associated with subcortical alterations and progression risk in subjective cognitive decline. *Alzheimers Res Ther*, in press 2023 **IF 8.823**

51. Čarna M, Onyango IG, Katina S, Holub D, Novotny JS, Nezvedova M, Jha D, **Nedelska Z**, Lacovich V, Vyvere TV, Houbrechts R, Garcia-Mansfield K, Sharma R, David-Dirgo V, Vyhnalek M, Texlova K, Chaves H, Bakkar N, Pertierra L, Vinkler M, Markova H, Laczo J, Sheardova K, Hortova-Kohoutkova M, Frič J, Forte G, Kaňovsky P, Belaškova S, Damborsky J, Hort J, Seyfried NT, Bowser R, Sevlever G, Rissman RA, Smith RA, Hajduch M, Pirrotte P, Spacil Z, Dammer EB, Limbäck-Stokin C, Stokin GB. Pathogenesis of Alzheimer's disease: Involvement of the choroid plexus. *Alzheimers Dement.* 2023 Feb 24. Epub ahead of print. **IF 21.566**

52. Reid RI, **Nedelska Z**, Schwarz CG, Ward C, Jack CR, for ADNI. Diffusion Specific Segmentation: Skull Stripping 1 with Diffusion MRI Data Alone. Book chapter, in Enrico Kaden et al, editors, Computational Diffusion MRI, *Mathematics and Visualization*. Springer, 2018 **IF 0.69, book chapter**

Peer-reviewed Czech or English language papers:

53. Gažová I., Vlček K., **Nedelská Z,** Mokrisova I, Hyncicova E, Laczo J, Hort J. , et al. (2012). Spatial navigation in physiological and pathological ageing. *Cesk. Slov. Neurol. N.* 75/108 (4): 411-414. **IF 0.311**

54. Kadlecová A., Vyhnálek M., Laczó J., Andel R., **Nedelská Z**., Sheardova K, Urbanmova B, Hudecek D, Gazova I, Lisy J, Hort J. (2013). Inter-rater variability in assessing hippocampal atrophy using Scheltens Scales. *Cesk. Slov. Neurol.* N. 76/109 (5): 603-607. **IF 0.508**

55. Vlček K., Levčík D, Nedělská Z, Laczó, J, Vyhnálek M.; Hort J. Prostorová navigace jako kognitivní doména v diagnostice mírné kognitivní poruchy (Spatial navigation as a cognitive domain in the diagnosis of mild cognitive impairment) Psychiatrie 2011, 12: 58-62 *no IF*

56. Vlček K, **Nedelská Z**, Laczo J, Vyhnalek M, Hortz J.Navigace v reálném prostoru ve vývoji Alzheimerovy choroby (Real space navigation in the development of Alzheimer's disease), Psychiatrie 2010, 14:52-55 *no IF*

57. Chen Q, Chen F, Long C, Lu J, Chen J, **Nedelska Z**, Hort J, Zhang B. Neuroimaging associations with spatial navigation impairment in Alzheimer's disease continuum: A narrative review. *Advanced Neurology* 2022, 1(2)145. *IF not assigned yet*

10.4. Presentations: Selected oral invited platforms

2022 International Dementia with Lewy Bodies Conference, Newcastle, UK: Imaging in dementia with Lewy bodies

2020 Advances in Alzheimer and Parkinson Therapies (AAT/ADPD), Vienna: Mild Cognitive Impairment Progressing to Dementia with Lewy bodies: Rates of Regional Atrophy and Associations with Clinical Decline

2019 International Conference on Alzheimer's Disease and Subjective Cognitive Decline, Nanjing, China: Multimodality imaging in prodrodromal AD and DLB

2019 Idiopathic REM sleep behavior disorder study group symposium (IRBDSG), Copenhagen: Ioflupane-SPECT Findings Using DaTQUANT in Patiens with Mild Cognitive Impairment and REM Sleep Behavior Disorder

2019 Alzheimer's Imaging Consortium, Alzheimer's Association International Conference, Los Angeles: Mild cognitive impairment progressing to Dementia with Lewy bodies: Longitudinal rates of atrophy and relationship to AV-1451 & PiB Uptake

2019 International Dementia with Lewy Bodies Conference (IDLBC), Las Vegas:

The Trajectory of Longitudinal Amyloid-β Accumulation on PiB PET and Association with Disease Progression in Dementia with Lewy Bodies

2018 Alzheimer's Imaging Consortium, Alzheimer's Association International Conference, Chicago: Longitudinal Accumulation of β-Amyloid on PET in Dementia with Lewy Bodies and Relationship to Clinical Disease Progression

2017 American Academy of Neurology (AAN), Boston: Tissue metabolites on1H-MRS at baseline are associated with a greater rate of β-amyloid accumulation on serial PET in clinically normal older adults

2016 Alzheimer's Association International Conference (AAIC), Toronto: Distinct spatial navigation impairment across neurodegenerative dementias and its neuroanatomical underpinnings

2014 American Academy of Neurology (AAN), Philadelphia: Longitudinal rates of atrophy in autopsy-confirmed dementia with Lewy bodies and associations with clinical and cognitive decline

10.5. Foreign fellowships and stays

5/2012-9/2012 – Research assistant, Department of Neurology, Psychology and Psychiatry, Mayo Clinic Scottsdale, USA

10/2012-6/2014 – Research fellow, Department of Neurology, Department of Radiology, Mayo Clinic Rochester, USA

9/2016-8/2019 – Senior research fellow, Department of Radiology, Division of Neuroradiology, Mayo Clinic Rochester, USA